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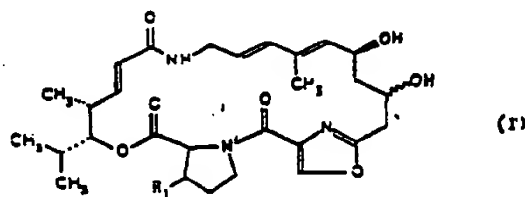
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(56) Documents cited  
 None

(58) Field of search  
 C2C

(54) Novel pristinamycin II<sub>8</sub> derivatives, their preparation and pharmaceutical compositions containing them

(57) Novel pristinamycin II<sub>8</sub> derivatives have the formula:



in which R<sub>1</sub> denotes a substituted alkylthio radical, a radical of formula Het-S-, a dialkylamino radical, a radical of formula R<sub>2</sub>-S- where R<sub>2</sub> is a substituted alkyl radical or a heterocyclic radical and n is 1 or 2 or an alkylamino radical.  
 (O)<sub>n</sub>

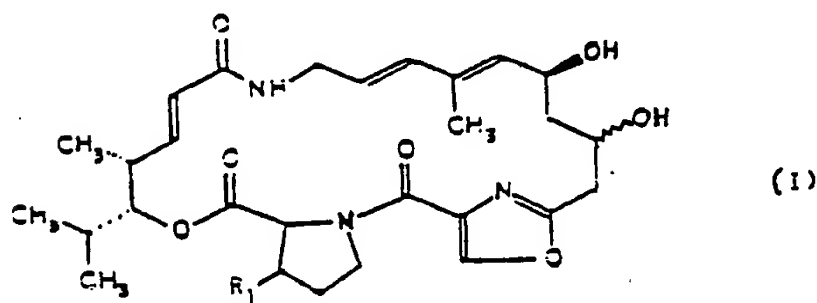
These compounds have useful antibacterial activity.

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"NEW COMPOSITIONS OF MATTER"

This invention relates to pristinamycin II<sub>B</sub> derivatives, their preparation, and compositions containing them.

The present invention provides new pristinamycin II<sub>B</sub> derivatives, of the formula:



in which R<sub>1</sub> denotes

1. an alkylthio radical containing 1 to 5 carbon atoms, substituted

- i) with one or two alkylamino or dialkylamino radicals in which the alkyl portions, which contain 1 to 5 carbon atoms, can optionally form, together with the nitrogen atom to which they are linked, a saturated heterocyclic radical chosen from 1-pyrrolidinyl, piperidino, 1-azetidyl, 1-azepinyl, morpholino, thiomorpholino and 1-piperazinyl (optionally substituted with an alkyl radical containing 1 to 5 carbon atoms), or alternatively

- ii) with a 2- or 3-pyrrolidinyl, 2-, 3- or 4-piperidyl, 2- or 3-azetidyl or 2-, 3- or 4-azepinyl

radical,

2. a radical of general formula:



in which Het denotes a 3-pyrrolidinyl, 3- or 4-piperidyl,  
5 3-azetidiny l or 3- or 4-azepiny l radical, optionally sub-  
stituted with an alkyl radical containing 1 to 5 carbon  
atoms,

3. a dialkylamino radical in which the alkyl portions,  
which contain 1 to 5 carbon atoms, can optionally form,  
10 together with the nitrogen atom to which they are linked,  
a saturated heterocyclic radical chosen from 1-pyrrolidinyl,  
piperidino, 1-azetidiny l, 1-azepiny l, morpholino, thio-  
morpholino and 1-piperaziny l (optionally substituted with  
an alkyl radical containing 1 to 5 carbon atoms),

15 4. a radical of general formula:



in which R<sub>2</sub> denotes

i) either a 4- to 7-membered nitrogen-containing  
20 heterocyclic radical optionally containing one or more  
other hetero atoms chosen from nitrogen, oxygen or sulphur  
in the state of sulfoxide or sulphone, and optionally  
substituted with an alkyl radical,

ii) or an alkyl chain containing 2 to 4 carbon  
25 atoms and substituted with 1 or 2 radicals chosen from  
phenyl, cycloalkylamino or N-alkyl-N-cycloalkylamino con-  
taining 3 to 6 ring atoms, alkylamino, dialkylamino or

dialkylcarbamoyloxy, the alkyl portions of these last 2 radicals optionally being able to form, with the nitrogen atom to which they are attached, a 4- to 7-membered saturated or unsaturated heterocyclic radical optionally containing another hetero atom chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, and optionally substituted with an alkyl radical), or substituted with one or more 4- to 7-membered nitrogen-containing heterocyclic radicals optionally containing 1 or 2 other hetero atoms chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, these heterocyclic radicals optionally being substituted with an alkyl radical, the said heterocyclic radicals being attached to the chain which bears them via a carbon atom, with the proviso that at least one of the substituents borne by the above alkyl chain is a nitrogen-containing substituent capable of forming salts, or [(S)-1-methyl-2-pyrrolidinyl]methyl, and the symbol n equals 1 or 2,

5. an alkylamino radical which is optionally substituted by a hydroxy (e.g. the 2-hydroxyethylamino radical) or alkylamino or

dialkylamin , the alkyl portions of this last radical optionally being able to form, with the nitrogen atom to which they are attached, a 4- to 7-membered saturated or unsaturated heterocyclic radical optionally containing another hetero atom chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, and optionally substituted with an alkyl radical), or substituted with one or more 4- to 7-membered nitrogen-containing heterocyclic radicals optionally containing 1 or 2 other hetero atoms chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, these heterocyclic radicals optionally being substituted with an alkyl radical, the said heterocyclic radicals being attached to the chain which bears them via a carbon atom,

with the proviso that the alkyl radicals and portions mentioned above are linear or branched and contain, except where otherwise stated, 1 to 10 carbon atoms.

The pristinamycin IIg derivatives of general formula (I) have isomeric forms and their isomers and their mixtures are included within the scope of the present invention.

The wavy line  $\sim$  indicates that the hydroxy group in the 16-position may be above (beta) or below (alpha) the plane of the ring system.

In the definition of the general formula (I),

section 4.,

when  $R_2$  denotes a heterocyclic radical, this radical can be chosen, by way of example, from 3-azetidiny, 3-pyrrolidiny, 3- or 4-piperidyl or 3- or 4-azepiny,

5      when  $R_2$  denotes an alkyl radical substituted with a heterocyclic radical, the heterocyclic radical can be chosen, by way of example, from the radicals mentioned above or a 2-azetidiny, 2-pyrrolidiny, 2-piperidyl, 2-azepiny, piperaziny, 4-alkylpiperaziny, quinoly, iso-  
10      quinoly or imidazolyl radical,

when  $R_2$  contains a dialkylamino or dialkylcarbamoyloxy radical in which the alkyl portions form a heterocyclic radical with the nitrogen atom to which they are

attached, this ring can be chosen, for example, from:

1-azetidiny, 1-pyrrolidinyl, piperidino, 1-azepiny, morpholino, thiomorpholino in the form of sulfoxide or sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl, or 1-imidazolyl.

The following compounds of general formula (I) can be mentioned, in particular, by way of example: 16-alcohols of

- 26-(3-azetidiny)sulphinypristinamycin IIg
- 26-(1-methyl-3-azetidiny)sulphinypristinamycin IIg
- 10 - 26-(1-ethyl-3-azetidiny)sulphinypristinamycin IIg
- 26-(1-isopropyl-3-azetidiny)sulphinypristinamycin IIg
- 26-(3-pyrrolidinyl)sulphinypristinamycin IIg
- 26-(1-methyl-3-pyrrolidinyl)sulphinypristinamycin IIg
- 26-(1-ethyl-3-pyrrolidinyl)sulphinypristinamycin IIg
- 15 - 26-(1-isopropyl-3-pyrrolidinyl)sulphinypristinamycin II
- 26-(3-piperidyl)sulphinypristinamycin IIg
- 26-(1-methyl-3-piperidyl)sulphinypristinamycin IIg
- 26-(1-ethyl-3-piperidyl)sulphinypristinamycin IIg
- 26-(4-piperidyl)sulphinypristinamycin IIg
- 20 - 26-(1-methyl-4-piperidyl)sulphinypristinamycin IIg
- 26-(1-ethyl-4-piperidyl)sulphinypristinamycin IIg
- 26-(3-azepiny)sulphinypristinamycin IIg
- 26-(4-azepiny)sulphinypristinamycin IIg
- 26-(2-cyclopropylaminoethyl)sulphinypristinamycin IIg
- 25 - 26-(2-cyclobutylaminoethyl)sulphinypristinamycin IIg
- 26-(2-cyclopentylaminoethyl)sulphinypristinamycin IIg
- 26-(2-cyclohexylaminoethyl)sulphinypristinamycin IIg

- 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-(2-methylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-ethylaminoethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-propylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-butylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 10 - 26-(dimethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diisopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylaminoethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-diisobutylaminoethyl)sulphonylpristinamycin IIg
- 26-(N-ethyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 20 - 26-(2-piperidinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azepinyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-morpholinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 25 mycin IIg
- 26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphonylpristinamycin IIg



- 26-[2-(1-imidazolyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-dimethylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 26-(2-diethylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-diisopropylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphonylpristinamycin IIg
- 10 - 26-[2-(2-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg
- 15 - 26-[2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azepinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azepinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-azepinyl)ethyl]sulphonylpristinamycin IIg
- 20 - 26-[2-(3-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-isoquinolyl)ethyl]sulphonylpristinamycin IIg
- 25 - 26-(2-imidazolethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylamino-1-methylethyl)sulphonylpristinamycin IIg

- 26-(2-cyclobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopentylamino-1-methylethyl)sulphonylpristinamycin IIg
- 5 - 26-(cyclohexylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-cyclohexyl-N-methylamino)-1-methylethyl]-sulphonylpristinamycin IIg
- 26-(2-methylamino-1-methylethyl)sulphonylpristinamycin
- 10 IIg
- 26-(2-ethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(1-methyl-2-propylaminoethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-isopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-butylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 20 mycin IIg
- 26-(1-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylamino-1-methylethyl)sulphonylpristinamycin IIg

- 26-(2-diisopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-diisobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-ethyl-N-methylamino)-1-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)-1-methylethyl]sulphonylpristinamycin IIg
- 10 - 26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-(1-methyl-2-piperidinoethyl)sulphonylpristinamycin IIg
- 15 - 26-[2-(1-azepinyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-(1-methyl-2-morpholinoethyl)sulphonylpristinamycin IIg
- 26-[1-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 20 - 26-[2-(4-methyl-1-piperazinyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]sulphonylpristinamycin IIg
- 25 - 26-[2-(1-imidazolyl)-1-methylethyl]sulphonylpristinamycin IIg

- 26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphinyl-pristinamycin IIg
- 26-(2-diethylaminocarbamoyloxy-1-methylethyl)sulphinyl-pristinamycin IIg
- 5 - 26-(2-diisopropylaminocarbamoyloxy-1-methylethyl)-sulphinylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphinylpristinamycin IIg
- 26-[2-(2-azetidiny)-1-methylethyl]sulphinylpristinamycin IIg
- 10 mycin IIg
- 26-[2-(3-azetidiny)-1-methylethyl]sulphinylpristinamycin IIg
- 26-[1-methyl-2-(2-pyrrolidinyl)ethyl]sulphinylpristinamycin IIg
- 15 - 26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphinylpristinamycin IIg
- 26-[1-methyl-2-(2-piperidyl)ethyl]sulphinylpristinamycin IIg
- 26-[1-methyl-2-(3-piperidyl)ethyl]sulphinylpristinamycin IIg
- 20 mycin IIg
- 26-[1-methyl-2-(4-piperidyl)ethyl]sulphinylpristinamycin IIg
- 26-[2-(2-azepinyl)-1-methylethyl]sulphinylpristinamycin IIg
- 25 - 26-[2-(3-azepinyl)-1-methylethyl]sulphinylpristinamycin IIg

- 26-[2-(4-azepinyl)-1-methylethyl]sulphonylpristinamycin  
IIg
- 26-[1-methyl-2-(3-quinolyl)ethyl]sulphonylpristina-  
mycin IIg
- 5 - 26-[1-methyl-2-(4-quinolyl)ethyl]sulphonylpristina-  
mycin IIg
- 26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-  
sulphonylpristinamycin IIg
- 26-[2-(1-isoquinolyl)-1-methylethyl]sulphonylpristina-  
10 mycin IIg
- 26-(2-imidazolyl-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylamino-2-methylethyl)sulphonylpristina-  
mycin IIg
- 26-(2-cyclobutylamino-2-methylethyl)sulphonylpristina-  
15 mycin IIg
- 26-(2-cyclopentylamino-2-methylethyl)sulphonylpristina-  
mycin IIg
- 26-(2-cyclohexylamino-2-methylethyl)sulphonylpristina-  
mycin IIg
- 20 - 26-[2-(N-cyclohexyl-N-methylamino)-2-methylethyl]-  
sulphonylpristinamycin IIg
- 26-(2-methylamino-2-methylethyl)sulphonylpristinamycin  
IIg
- 26-(2-ethylamino-2-methylethyl)sulphonylpristinamycin  
25 IIg
- 26-(2-methyl-2-propylaminoethyl)sulphonylpristinamycin  
IIg

- 26-(2-isopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-butylamino-2-methylethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-isobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 10 - 26-(2-diethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-diisopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-diisobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 20 - 26-[2-(N-ethyl-N-methylamino)-2-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)-2-methylethyl]sulphonylpristinamycin IIg
- 25 - 26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-methyl-2-piperidinoethyl)sulphonylpristinamycin IIB

- 26-[2-(1-azepinyl)-2-methylethyl]sulphinylpristinamycin  
IIg
- 26-(2-methyl-2-morpholinoethyl)sulphinylpristinamycin  
IIg
- 5 - 26-[2-methyl-2-(1-piperazinyl)ethyl]sulphinylpristina-  
mycin IIg
- 26-[2-(4-methyl)-1-piperazinyl]-2-methylethyl]sulphinyl-  
pristinamycin IIg
- 26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]sulphinyl-  
10 pristinamycin IIg
- 26-[2-(1-imidazolyl)-2-methylethyl]sulphinylpristina-  
mycin IIg
- 26-(2-dimethylaminocarbamoyloxy-2-methylethyl)sulphinyl-  
pristinamycin IIg
- 15 - 26-(2-diethylaminocarbamoyloxy-2-methylethyl)sulphinyl-  
pristinamycin IIg
- 26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)sulphinyl-  
pristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methyl-  
20 ethyl]sulphinylpristinamycin IIg
- 26-[2-(2-azetidiny)-2-methylethyl]sulphinylpristina-  
mycin IIg
- 26-[2-(3-azetidiny)-2-methylethyl]sulphinylpristina-  
mycin IIg
- 25 - 26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphinylpristina-  
mycin IIg

- 26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg
- 5 - 26-[2-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 10 - 26-[2-(3-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(4-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 15 - 26-[2-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin IIg
- 20 - 26-[2-(1-isoquinolyl)-2-methylethyl]sulphonylpristinamycin IIg
- 26-(imidazolyl-2-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-dimethylamino-3-phenylpropyl)sulphonylpristinamycin IIg
- 26-(2-dimethylaminobutyl)sulphonylpristinamycin IIg



- 26-(3-azetidinyI)sulphonylpristinamycin IIg
- 26-(1-methyl-3-azetidinyI)sulphonylpristinamycin IIg
- 26-(1-ethyl-3-azetidinyI)sulphonylpristinamycin IIg
- 26-(1-isopropyl-3-azetidinyI)sulphonylpristinamycin IIg
- 5 - 26-(3-pyrrolidinyl)sulphonylpristinamycin IIg
- 26-(1-methyl-3-pyrrolidinyl)sulphonylpristinamycin IIg
- 26-(1-ethyl-3-pyrrolidinyl)sulphonylpristinamycin IIg
- 26-(1-isopropyl-3-pyrrolidinyl)sulphonylpristinamycin IIg
- 10 - 26-(3-piperidyl)sulphonylpristinamycin IIg
- 26-(1-methyl-3-piperidyl)sulphonylpristinamycin IIg
- 26-(1-ethyl-3-piperidyl)sulphonylpristinamycin IIg
- 26-(4-piperidyl)sulphonylpristinamycin IIg
- 26-(1-methyl-4-piperidyl)sulphonylpristinamycin IIg
- 15 - 26-(1-ethyl-4-piperidyl)sulphonylpristinamycin IIg
- 26-(3-azepinyl)sulphonylpristinamycin IIg
- 26-(4-azepinyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-cyclobutylaminoethyl)sulphonylpristinamycin IIg
- 20 - 26-(2-cyclopentylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-cyclohexylaminoethyl)sulphonylpristinamycin IIg
- 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-(2-methylaminoethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-ethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-propylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isopropylaminoethyl)sulphonylpristinamycin IIg

- 26-(2-butylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylaminoethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-diethylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diisopropylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-diisobutylaminoethyl)sulphonylpristinamycin IIg
- 10 - 26-(N-ethyl-N-methyl-2-aminoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 15 - 26-(2-piperidinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azepinyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-morpholinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 20 - 26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-imidazolyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-dimethylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-diethylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg

- 26-(2-diisopropylaminocarbamoyloxyethyl)sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphonylpristinamycin IIg
- 5 - 26-[2-(2-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azetidiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg]
- 10 - 26-[2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azepiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azepiny)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-azepiny)ethyl]sulphonylpristinamycin IIg
- 15 - 26-[2-(3-quinoly)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-quinoly)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1,2,3,4-tetrahydro-2-isoquinoly)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-isoquinoly)ethyl]sulphonylpristinamycin IIg
- 20 - 26-(2-imidazolylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-cyclopentylamino-1-methylethyl)sulphonylpristinamycin IIg

- 26-(2-cyclohexylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-cyclohexyl-N-methylamino)-1-methylethyl]-sulphonylpristinamycin IIg
- 5 - 26-(2-methylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-ethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(1-methyl-2-propylaminoethyl)sulphonylpristinamycin IIg
- 10 - 26-(2-isopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-butylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-isobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 15 - 26-(1-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 20 - 26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-diisopropylamino-1-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-dibutylamino-1-methylethyl)sulphonylpristinamycin IIg

- 26-(2-diisobutylamino-1-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-ethyl-N-methylamino)-1-methylethyl]sulphonylpristinamycin IIg
- 5 - 26-[2-(1-(azetidinyI)-1-methylethyl]sulphonylpristinamycin IIg
- 26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-(1-methyl-2-piperidinoethyl)sulphonylpristinamycin
- 10 IIg
- 26-[2-(1-azepinyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-(1-methyl-2-morpholinoethyl)sulphonylpristinamycin IIg
- 15 - 26-[1-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]-
- 20 sulphonylpristinamycin IIg
- 26-[2-(1-imidazolyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-diethylaminocarbamoyloxy)-1-methylethyl)-sulphonylpristinamycin IIg

- 26-(2-diisopropylaminocarbamoyloxy-1-methylethyl)-sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphonylpristinamycin IIg
- 5 - 26-[2-(2-azetidinyI)-1-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azetidinyI)-1-methylethyl]sulphonylpristinamycin IIg
- 26-[1-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 10 - 26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-[1-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg
- 15 - 26-[1-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[1-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azepinyI)-1-methylethyl]sulphonylpristinamycin IIg
- 20 - 26-[2-(3-azepinyI)-1-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(4-azepinyI)-1-methylethyl]sulphonylpristinamycin IIg
- 25 - 26-[1-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin IIg

- 26-[1-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin IIg
- 5 - 26-[2-(1-isoquinolyl)-1-methylethyl]sulphonylpristinamycin IIg
- 26-(2-imidazolyl-1-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 10 - 26-(2-cyclobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclopentylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-cyclohexylamino-2-methylethyl)sulphonylpristinamycin IIg
- 15 - 26-[2-(N-cyclohexyl-N-methylamino)-2-methylethyl]-sulphonylpristinamycin IIg
- 26-(2-methylamino-2-methylethyl)sulphonylpristinamycin IIg
- 20 - 26-(2-ethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-methyl-2-propylaminoethyl)sulphonylpristinamycin IIg
- 26-(2-isopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 25 - 26-(2-butylamino-2-methylethyl)sulphonylpristinamycin IIg

- 26-(2-isobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-methyl-2-n-decylaminoethyl)sulphonylpristinamycin IIg
- 5 - 26-(2-dimethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-diethylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dipropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 10 - 26-(2-diisopropylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dibutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 15 - 26-(2-diisobutylamino-2-methylethyl)sulphonylpristinamycin IIg
- 26-[2-(N-ethyl-N-methylamino)-2-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(1-azetidiny)-2-methylethyl]sulphonylpristinamycin IIg
- 20 - 26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin IIg
- 26-(2-methyl-2-piperidinoethyl)sulphonylpristinamycin IIg
- 26-[2-(1-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg



- 26-(2-methyl-2-morpholinoethyl)sulphonylpristinamycin  
IIg
- 26-[2-methyl-2-(1-piperazinyl)ethyl]sulphonylpristina-  
mycin IIg
- 5 - 26-[2-(4-methyl-1-piperazinyl)-2-methylethyl]sulphonyl-  
pristinamycin IIg
- 26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]-  
sulphonylpristinamycin IIg
- 26-[2-(1-imidazolyl)-2-methylethyl]sulphonylpristina-  
10 mycin IIg
- 26-(2-dimethylaminocarbamoyloxy-2-methylethyl)sulphonyl-  
pristinamycin IIg
- 26-(2-diethylaminocarbamoyloxy-2-methylethyl)sulphonyl-  
pristinamycin IIg
- 15 - 26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)-  
sulphonylpristinamycin IIg
- 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methyl-  
ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azetidiny)l)-2-methylethyl]sulphonylpristina-  
20 mycin IIg
- 26-[2-(3-azetidiny)l)-2-methylethyl]sulphonylpristina-  
mycin IIg
- 26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristina-  
mycin IIg
- 25 - 26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristina-  
mycin IIg

- 26-[2-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin IIg
- 5 - 26-[2-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(2-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 26-[2-(3-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 10 - 26-[2-(4-azepinyl)-2-methylethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin IIg
- 15 - 26-[2-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]sulphonylpristinamycin IIg
- 26-[2-(1-isoquinolyl)-2-methylethyl]sulphonylpristinamycin IIg
- 20 - 26-(2-imidazolyl-2-methylethyl)sulphonylpristinamycin IIg
- 26-(2-dimethylamino-3-phenylpropyl)sulphonylpristinamycin IIg
- 25 - 26-(2-dimethylaminobutyl)sulphonylpristinamycin IIg

and the 26-thio analogues thereof e.g. 16-alcohols of  
26-(1-diethylaminoprop-2-yl)thio-pristinamycin II<sub>B</sub>,  
as well as 16-alcohols of 26-(2-hydroxyethylamino)- and  
26-(4-methylpiperazin-1-yl)-pristinamycin II<sub>B</sub> and

5 especially

Compound No.

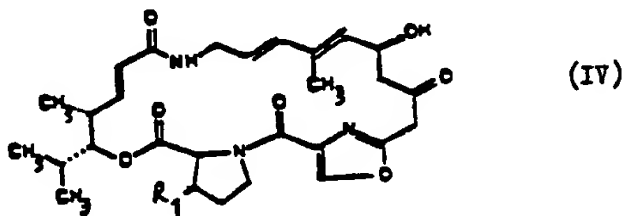
1. 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16alpha-  
hydroxypristinamycin II<sub>B</sub> (isomer A)
2. 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16beta-  
10 hydroxypristinamycin II<sub>B</sub> (isomer A)
3. 16-deoxy-26-(2-diisopropylaminoethyl)thio-16alpha-  
hydroxypristinamycin II<sub>B</sub> (isomer A)
4. 16-deoxy-26-(2-diisopropylaminoethyl)thio-16beta-  
hydroxypristinamycin II<sub>B</sub> (isomer A)
- 15 5. 16-deoxy-26-(2-diisopropylaminoethyl)sulphinyl-  
16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>)
6. 16-deoxy-26-(2-diisopropylaminoethyl)sulphinyl-  
16beta-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>)
7. 16-deoxy-26-(2-diethylaminoethyl)thio-16beta-hydroxy-  
20 pristinamycin II<sub>B</sub> (isomer A)
8. 16-deoxy-26-(2-diethylaminoethyl)thio-16alpha-  
hydroxypristinamycin II<sub>B</sub> (isomer A)
9. 16-deoxy-26-(2-diethylaminoethyl)sulphinyl-16alpha-  
hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>)
- 25 10. 16-deoxy-26-(2-diethylaminoethyl)sulphinyl-16alpha-  
hydroxypristinamycin II<sub>B</sub> (isomers A<sub>1</sub> + A<sub>2</sub>)

11. 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16beta-hydroxypristinamycin (isomer A<sub>2</sub>)
12. 16-deoxy-26-ethylamino-16beta-hydroxypristinamycin II<sub>B</sub> (isomer A)
- 5 13. 16-deoxy-26-ethylamino-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A)
14. 16-deoxy-26-(2-diethylaminoethyl)amino-16alpha-hydroxypristinamycin II<sub>B</sub>
15. 16-deoxy-26-(2-diethylaminoethyl)amino-16beta-hydroxypristinamycin II<sub>B</sub>
- 10 and isomers and salts thereof.

The numbers 1 to 15 are assigned to the compounds for easy reference, later in the specification, for example in the Examples.

The compounds of general formula (I) may be prepared by the application or adaptation of known methods (i.e. methods heretofore used or described in the chemical literature).

- 5 According to the present invention, the products of general formula (I) may be prepared by reduction of a compound of the general formula:-



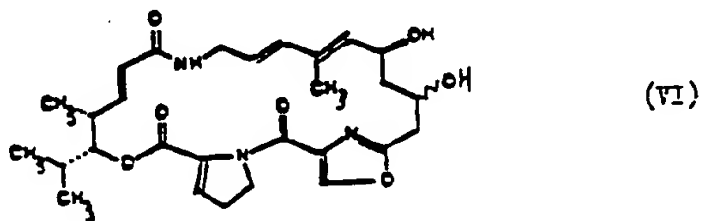
where  $R_1$  is as hereinbefore defined.

The reaction may be carried out using sodium  
10 borohydride in an inert organic solvent, e.g. an alcohol, for example methanol, at ambient temperature.

According to a further feature of the present invention the products of general formula (I) in which  $R_1$  does not represent a radical of general formula (III) may be  
15 prepared by the reaction of a product of general formula:



in which  $R_1^1$  is defined as above for  $R_1$  with the proviso that it does not represent  $R_2-S(O)_n-$  with a product of formula:



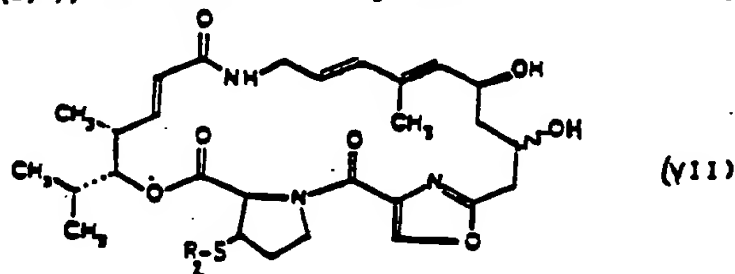
that is to say a pristinamycin II<sub>A</sub> 16-alcohol,  
described by Le Goffic.

The reaction may be carried out in a similar manner  
to that described in European Patent Publication EP  
5 135410 in an organic solvent such as an alcohol such as  
methanol or ethanol, or a chlorinated solvent such as  
methylene chloride, 1,2-dichloroethane or chloroform,  
or in a mixture of these solvents (for example  
methylene chloride/methanol) at a temperature between  
10 -30 and 50°C, optionally under nitrogen or argon. When  
R<sub>1</sub> is a substituted thio radical it is preferred to carry  
out the reaction in alcohol in presence of an alkali  
metal alkoxide.

Occasionally it may be advantageous to operate in  
15 the presence of a tertiary amine, for example  
triethylamine, or of an ethanolamine (for example  
dimethylethanolamine).

A person skilled in the art will understand that,  
when R<sub>1</sub><sup>'</sup> denotes a radical containing a secondary  
20 amine group capable of interfering with the reaction,  
this group will need to be protected beforehand, before  
the product of general formula (V) is reacted with the  
product of formula (VI). Any usual means which enables  
a secondary amine function to be blocked in the form of  
25 a labile radical can be used for this purpose. It is  
especially advantageous to use the trifluoroacetyl  
radical as a blocking radical which can be removed as  
described below. In such a case, however, it is not  
absolutely essential to remove the protective radical,  
30 and the protected derivative can be used directly in  
the oxidation reaction.

According to a further feature of the present invention, the products of general formula (I) in which  $R_1$  represents a radical of general formula (III) where  $n = 1$  may be prepared by oxidation of a derivative of pristnamycin  $II_B$  (some of which are compounds of general formula (I)), of its salt or of a protected derivative, of general formula:

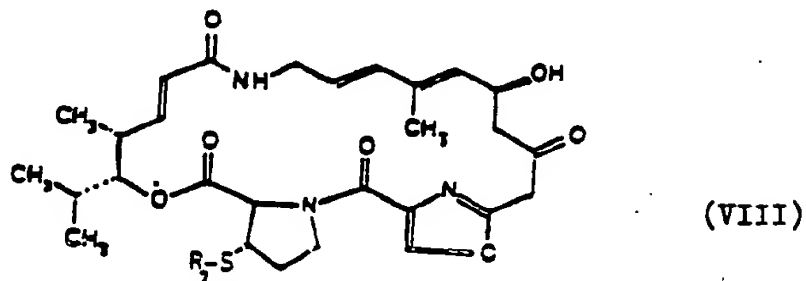


in which  $R_2$  is defined as above, it being understood that in the cases where  $R_2$  contains a sulphur-containing heterocyclic ring, the sulphur atom can be in the form of a sulphide, sulfoxide or sulphone.

10 The reaction is generally carried out by means of an oxidizing agent, optionally prepared in situ, in an aqueous medium or in an organic solvent, preferably a chlorinated solvent (methylene chloride, 1,2-dichloroethane or chloroform, for example) or an alcohol (methanol or tert-butanol, for example) or a mixture of these sol-  
15 vents. Optionally the operation can be carried out under nitrogen.

Among the oxidizing agents which are suitable for preparing a product of general formula (I) in which  
20  $n = 1$ , it is possible to mention organic peracids: percarboxylic or persulphonic acids (for example peracetic, pertrifluoroacetic, performic, perbenzoic, m-chloroperbenzoic, p-nitroperbenzoic, permaleic, monoperphthalic, percamphoric or p-toluenepersulphonic acids) or inorganic  
25 peracids (for example periodic or persulphuric acid), or potassium peroxymonosulphate.

The compounds of general formula (IV) in which  $R_1$  represents a radical of general formula (III) may be prepared by oxidation of a derivative of pristnamycin IIg, of its salt or of a protected derivative, of general formula:



in which  $R_2$  is defined as above, it being understood that in the cases where  $R_2$  contains a sulphur-containing heterocyclic ring, the sulphur atom can be in the form of a sulphide, sulfoxide or sulphone.

The reaction is generally carried out by means of an oxidizing agent, optionally prepared in situ, in an aqueous medium or in an organic solvent, preferably a chlorinated solvent (methylene chloride, 1,2-dichloroethane or chloroform, for example) or an alcohol (methanol or tert-butanol, for example) or a mixture of these solvents. Optionally the operation can be carried out under nitrogen.

Among the oxidizing agents which are suitable for preparing a product of general formula (IV) in which  $n = 1$ , it is possible to mention organic peracids: percarboxylic or persulphonic acids (for example peracetic, pertrifluoroacetic, performic, perbenzoic, m-chloroperbenzoic, p-nitroperbenzoic, permaleic, monoperphthalic, percamphoric or p-toluenepersulphonic acids) or inorganic



peracids (for example periodic or persulphuric acid).

When the intention is to prepare a product of general formula (IV) in which  $n = 2$ , the operation is advantageously carried out in the presence of selenium dioxide and hydrogen peroxide, using the salt of the product of general formula (VIII), or in the presence of a peracid such as those referred to above, especially pertrifluoroacetic acid, or m-chloroperbenzoic acid.

When the derivative of pristinamycin IIg of general formula (VIII) is used in the form of a salt, use is made of the salts formed with organic or inorganic acids, preferably with trifluoroacetic, tartaric, acetic, benzoic or hydrochloric acids.

When the product of general formula (VIII) is used in the form of a salt or of a protected derivative, the reaction is advantageously carried out at a temperature between  $-40$  and  $50^{\circ}\text{C}$ .

When it is intended to prepare a product of general formula (IV) in which  $n = 1$ , it is also advantageous to operate by starting from the derivative of pristinamycin IIg of general formula (VIII) in the presence of an alkali metal bicarbonate (for example sodium bicarbonate) at a temperature between  $-60$  and  $-40^{\circ}\text{C}$ .

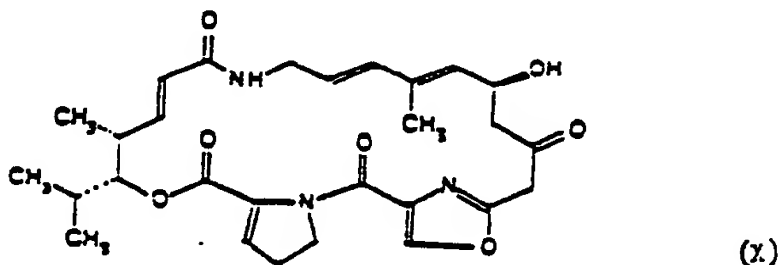
When  $R_2$  contains an alkylamino or cycloalkylamino substituent, it is also possible to utilize a protected derivative of the product of general formula (VIII). The latter can be protected by any amine-protective group

whose introduction and removal do not affect the remainder of the molecule; use is advantageously made of the trifluoroacetyl group which can be removed after the reaction by treatment with an alkali metal bicarbonate (sodium or potassium bicarbonate) in an aqueous solution.

The products of general formula (VIII) can be prepared by the reaction of a product of general formula:



in which  $\text{R}_2$  is defined as above, with the product of formula:



that is to say pristinamycin II<sub>A</sub>.

The reaction is usually carried out in an organic solvent such as an alcohol such as methanol or ethanol, or a chlorinated solvent such as methylene chloride, 1,2-dichloroethane or chloroform, or in a mixture of these solvents (for example methylene chloride/methanol) at a temperature between -30 and 50°C.

Occasionally it may be advantageous to operate in the presence of a tertiary amine, for example triethylamine, or of an ethanolamine (for example dimethylethanolamine)

A person skilled in the art will understand that, when R denotes a radical containing a secondary amine group capable of interfering with the reaction, this group will need to be protected beforehand, before the product of general formula (IX) is reacted with the product of formula (X). Any usual means which enables a secondary amine function to be blocked in the form of a labile radical can be used for this purpose. It is especially advantageous to use the trifluoroacetyl radical as a blocking radical which can be removed as described above. In such a case, however, it is not absolutely essential to remove the protective radical, and the protected derivative can be used directly in the oxidation reaction.

The products of general formula (IV) in which n is equal to 2 can also be prepared by the oxidation of a product of general formula (IV) in which n is equal to 1.

The reaction is carried out under conditions which are similar to the conditions described above for preparing a product of general formula (IV) in which n = 2 starting from a pristinamycin IIg derivative of general formula (VII).

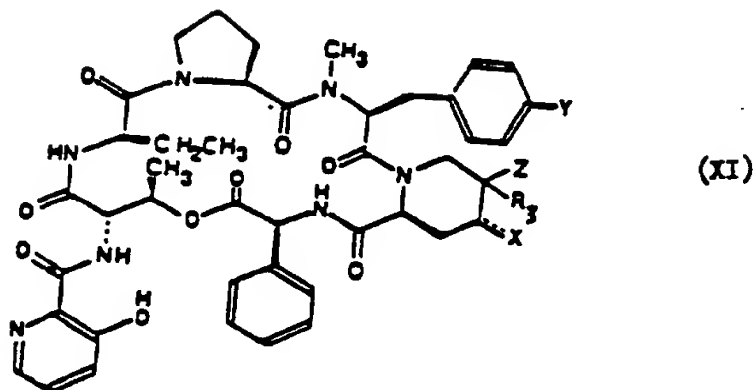
The new products of general formula (I) can be purified by known methods, for example by crystallization, chromatography or successive extractions in an acidic or basic medium. For the person skilled in the art who is

aware of the sensitivity of synergistins in an alkaline medium, a "basic medium" is understood to mean a medium which is just alkaline enough to liberate the parent substance from its salt of addition with an acid, that is to say a medium whose pH does not exceed 8.

It is well known that the synergistins obtained by fermentation constitute products which are greatly sought after by medical practitioners for the treatment of many complaints due to Gram-positive bacteria (of the Staphylococci, Streptococci, pneumococci or enterococci type) and Gram-negative bacteria (of the Haemophilus, gonococci, meningococci type). However, these products have the disadvantage of being insoluble in an aqueous medium and consequently can be administered only by oral route, generally in the form of gelatine capsules, coated pills or tablets. In view of this insolubility, it has hitherto been impossible to use the known synergistins when the patient is unable to swallow; this is the case, in particular, in paediatrics and in reanimation, while the activity spectrum of these products would render them a valuable indication in many circumstances, for example in cases of comatose septicaemias.

The new products according to the invention have the considerable advantage of being capable of being dissolved in water, usually in the form of salts, in usable therapeutic doses, and of enhancing, via a synergism phenomenon, the antibacterial action of pristinamycin Ia,

virginiamycin S or of soluble synergistin derivatives  
of general formula:



5 in which Y denotes a hydrogen atom or a dimethylamino radical and

1) either --- denotes a single bond, Z and R<sub>3</sub> denote a hydrogen atom and X denotes a radical of general formula:



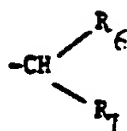
10 in which:

- either R<sub>4</sub> denotes a hydrogen atom and R<sub>5</sub> denotes a hydroxy or alkyl radical optionally substituted by a carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom  
15 to which they are attached, a 4 to 7-membered hetero-cyclic ring chosen from azetidiny, pyrrolidiny, piperidiny, piperaziny, N-alkylpiperaziny or azepiny rings, or R<sub>5</sub> denotes a cycloalkyl radical containing 3 to 7 carbon atoms

- or a saturated 4 to 7-membered heterocyclic ring chosen  
5 from the azetidine, pyrrolidine, piperidine and azepine  
rings, these heterocyclic rings being optionally capable  
of being substituted by an alkyl radical on the nitrogen  
atom,  
- or  $R_4$  denotes a formyl or alkylcarbonyl radical and  $R_5$   
10 denotes an alkyl radical substituted by a carboxy, alkyl-  
amino or dialkylamino radical whose alkyl radicals can  
form, with the nitrogen atom to which they are attached a 4,  
to 7-membered heterocyclic ring chosen from azetidiny,   
pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl  
15 or azepinyl ring, or  $R_5$  denotes a 4 to 7-membered hetero-  
cyclic ring chosen from the azetidine, pyrrolidine, piper-  
idine and azepine rings, these heterocyclic rings being  
capable of being substituted by an alkyl radical on the  
nitrogen atom,  
20 - or  $R_4$  and  $R_5$ , which are identical or different, denote an  
alkyl radical optionally substituted by a carboxy, alkyl-  
oxycarbonyl, hydroxy, alkylamino or dialkyl-amino radical  
whose alkyl radicals optionally form, with the nitrogen  
atom to which they are attached, a 4 to 7-membered hetero-  
25 cyclic ring chosen from azetidiny, pyrrolidinyl, piperi-  
dinyl, piperazinyl, N-alkylpiperazinyl or azepinyl  
- or  $R_4$  and  $R_5$  form, together with the nitrogen atom to  
which they are attached, a 4 to 7-membered heterocyclic  
ring chosen from the azetidine, pyrrolidine, piperidine,  
30 morpholine and piperazine rings, optionally substituted

by an alkyl radical,

2) or --- denotes a double bond, X denotes an oxygen atom and Z denotes a radical of general formula:



(XIII)

5 defined as follows:

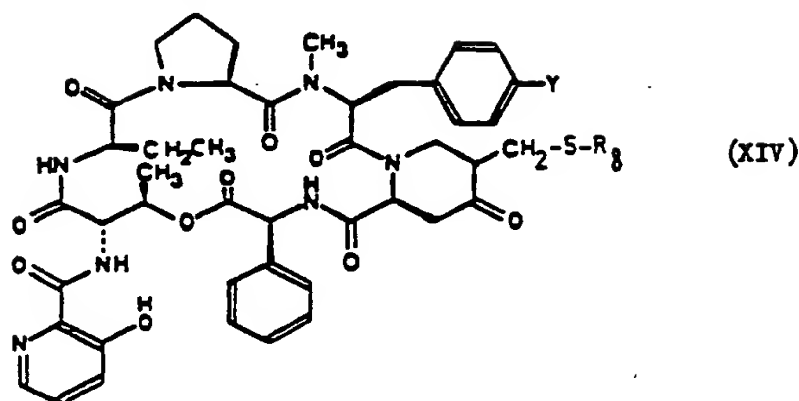
a) either  $\text{R}_3$  and  $\text{R}_7$  each denote a hydrogen atom and  $\text{R}_6$  denotes a 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical) or  $\text{R}_6$  denotes an alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino, or dialkylamino (optionally substituted by a mercapto or dialkylamino radical) radicals, or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical) morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidyl and 2- or 3-pyrrolidinyl radicals (the latter two rings being optionally substituted by an alkyl radical on the nitrogen atom),

b) or  $\text{R}_3$  and  $\text{R}_7$  together form a valency bond and  $\text{R}_6$  denotes a 3-pyrrolidinylamino, 3- or 4-piperidylamino, 3-pyrrolidinylloxy, 3- or 4-piperidylloxy, 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical on the nitrogen atom in the ring), or  $\text{R}_6$  denotes an alkylamino,

alkyloxy or alkylthio radical substituted by one or two hydroxy-sulphonyl, alkylamino, dialkylamino (optionally substituted by a dialkylamino radical), trialkylammonio or 4- or 5-imidazolyl radicals or by one or two rings  
5 chosen from piperazino (optionally substituted by an alkyl or mercapto alkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidinyl and 2- or 3-pyrro-lidinyl radical (the last two rings being optionally sub-stituted by an alkyl radical on the nitrogen  
10 atom), it being understood that the alkyl radicals and alkyl moieties referring to the symbols of the general formula (XI) contain 1 to 5 carbon atoms and form a linear or branched chain, or



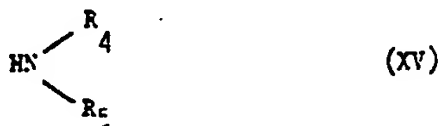
derivatives of the general formula:



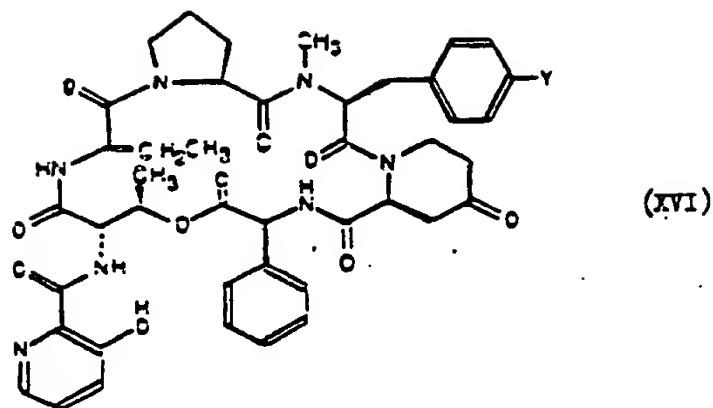
in which the symbol Y denotes a hydrogen atom or a dimethylamino radical and the symbol  $R_8$  denotes a 3- or 4-quinuclidinyl radical, or salts thereof.

Some of the derivatives of synergistins of formulae (XI) and (XIV) can have isomeric forms. It is to be understood that these isomeric forms as well as their mixtures can be advantageously associated with the products of general formula (1).

The products of general formula (XI) defined as above under 1), with the exception of those in which  $R_4$  denotes a formyl or alkylcarbonyl radical, can be prepared by the action of an amine of general formula:



in which  $R_4$  and  $R_5$  are defined as above, on a synergistin of general formula:



in which Y denotes a hydrogen atom (virginiamycin S) or the dimethylamino radical (pristinamycin I<sub>A</sub>), in the presence of an alkali metal cyanoborohydride.

5           The operation is generally carried out with an excess of amine of general formula (XV) in the presence of an alkali metal cyanoborohydride such as sodium cyanoborohydride, in an organic solvent such as an alcohol containing dissolved gaseous hydrogen chloride (methanolic  
10 hydrogen chloride or ethanolic hydrogen chloride) at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20°C.

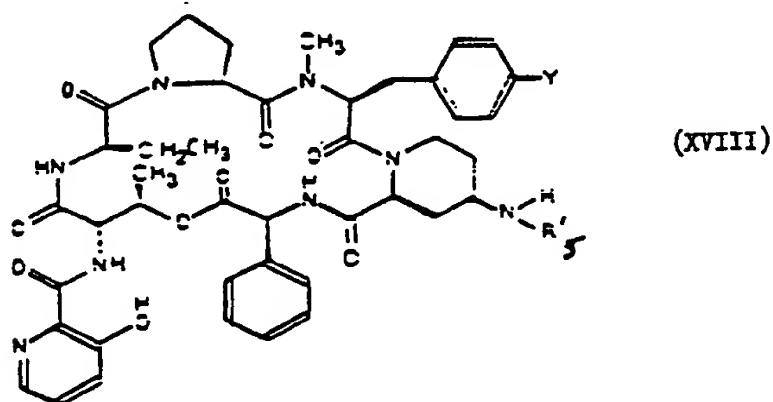
          The reaction can be advantageously carried out in  
15 the presence of a drying agent such as molecular sieves.

          The products of general formula (XI) defined as above under 1) in which R<sub>4</sub> denotes a formyl or alkylcarbonyl radical and R<sub>5</sub> denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals optionally form, with the nitrogen atom to  
20

which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidiny, pyrrolidiny, piperidiny, piperazinyl, alkyl-piperazinyl or azepiny ring, or denotes a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these hetero-cyclic rings being capable of being substituted by an alkyl radical on the nitrogen atom, and Y is defined as above, can be prepared by the action of a product of general formula:



in which  $R_9$  denotes a hydrogen atom or an alkyl radical and Q denotes a halogen atom or an alkylcarbonyloxy radical, on a product of general formula:



15 in which Y is defined as before and  $R'_5$  has the corresponding definition of  $R_5$  which is given above.

The reaction is usually carried out in an organic solvent such as pyridine, in a chlorinated solvent (methylene chloride) or an ether (tetrahydrofuran) in the presence

of an acid acceptor such as an organic base such as triethylamine or an inorganic base such as an alkali metal carbonate or bicarbonate such as sodium bicarbonate, the operation being carried out at a temperature between 0  
5 and 80°C.

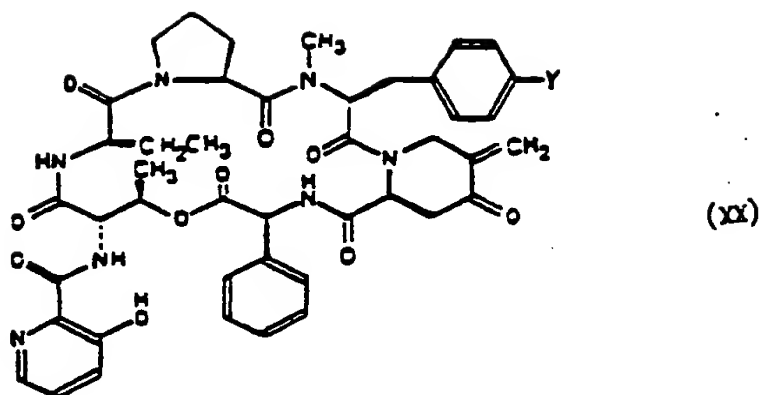
It is to be understood that, when R'5 denotes a radical containing a secondary amine group, the said group must be protected before the product of general formula (XVII) is reacted with the product of general formula (XVIII)  
10 The protection is carried out under the conditions described earlier for the preparation of the product of the general formula (VIII).

It is also to be understood that, when R4 and/or R5 in the general formula (XV) denote a radical containing a secondary amine group, the latter must be protected beforehand, before the product of general formula (XV) is reacted with the product of general formula (XVI). The blocking and the deblocking are carried out as described earlier.

20 The products of general formula (XI) defined as before under 2), in which Y is defined as before and the other symbols are defined as before under 2) a) can be prepared by the action of a product of general formula:



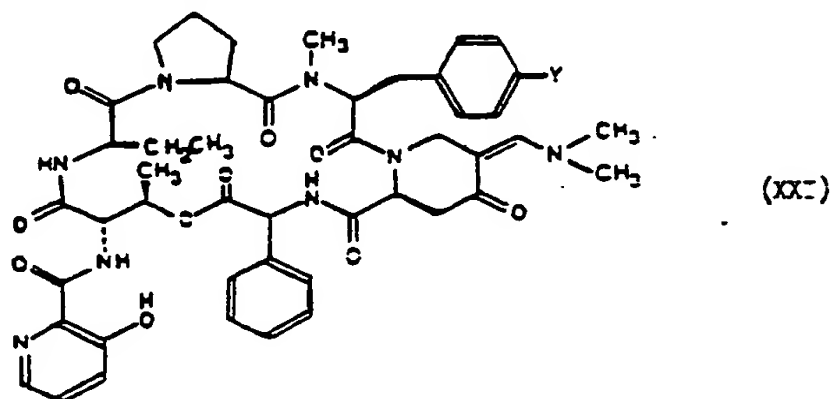
25 in which R'6 has the definition of R6 given earlier under 2) a), on the product of general formula:



in which Y is defined as before.

The operation is usually carried out in an organic solvent such as an alcohol such as methanol, or a chlorinated solvent such as chloroform, or a mixture of these solvents, at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20°C.

The products of general formula (XX) can be prepared by the action of an alkali metal borohydride such as sodium cyanoborohydride on a product of general formula:



in which Y is defined as before.

The operation is usually carried out in an organic

solvent such as an ether such as tetrahydrofuran, or an alcohol, for example isopropanol, in the presence of an acid such as trifluoroacetic acid, at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20°C.

The products of general formula (XXI) can be obtained by the action of a product of formula:



in which either X<sub>1</sub> denotes an alkyloxy radical and X<sub>2</sub> denotes an alkyloxy or dimethylamino radical, or X<sub>1</sub> and X<sub>2</sub> both denote a dimethylamino radical, on a product of general formula (XVI).

In practice, it is advantageous to react tert-butoxybis(dimethylamino)methane with the product of general formula (XVI), the operation being carried out in an organic solvent such as a chlorinated solvent such as 1,2-dichloroethane, or an amide (for example dimethylformamide) at a temperature between 0 and 80°C, preferably at a temperature in the region of 20°C.

The products of general formula (XXII) can be prepared according to the methods described by H. Bredereck et al., Chem. Ber., 101, 41 and 3058 (1968) and Chem. Ber., 106, 3725 (1973).

The products of general formula (XI) in which Y is defined as before and the other symbols are defined as earlier under 2) b), except for  $R_6$  denoting a 3-pyrrolidinyloxy, 3- or 4-piperidyloxy or alkyloxy radical, optionally substituted as defined under 2) b), can be prepared by the action of a product of general formula:



in which  $R''_6$  has the definition of  $R_6$  given above, on a product of general formula (XXI) in which Y is defined as earlier.

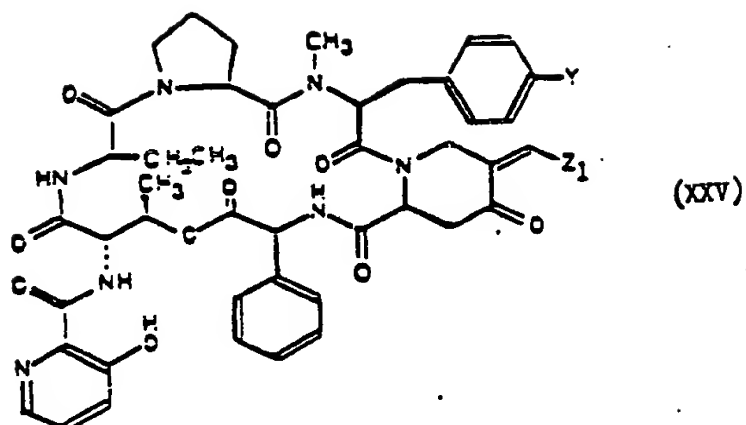
The reaction is carried out in an organic medium in the presence of an acid (for example acetic acid or a mixture of acetic acid with catalytic quantities of trifluoroacetic acid), in the presence or absence of a solvent, at a temperature between 0 and 50°C; preferably at a temperature in the region of 20°C.

Where applicable, the solvent can be chosen from organic solvents such as ethers (tetrahydrofuran), alcohols (ethanol) and chlorinated solvents (methylene chloride or chloroform, for example).

The products of general formula (XI) in which Y is defined as before and the other symbols are defined as earlier under 2) b) can be prepared by the action of a product of general formula:



in which  $R'''_6$  is defined as  $R_6$  under 2) b), on a product of general formula:



in which Y is defined as before and Z<sub>1</sub> denotes a tosyloxy, acetyloxy, trimethylsilyloxy or dialkyloxyphosphoryloxy radical whose alkyl moieties contain 1 to 4 carbon atoms forming a linear or branched chain or Z<sub>1</sub> denotes a chlorine atom.

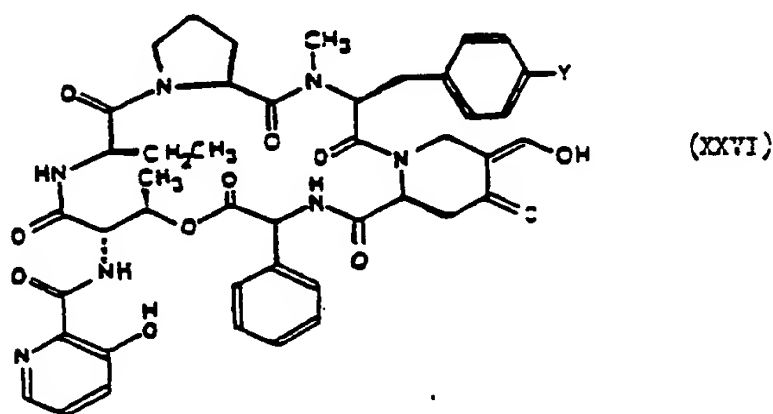
The operation is usually carried out in an organic solvent such as an ether such as tetrahydrofuran, an alcohol such as ethanol, or a chlorinated solvent (methylene chloride or chloroform, for example) at a temperature in the region of 20°C. The reaction is carried out in a basic medium, for example in the presence of an alkali metal hydride or an alkali metal alcoholate such as sodium ethoxide or potassium tert-butoxide.

When R''<sub>6</sub> is different from a substituted alkyloxy or (heterocyclic ring radical)oxy radical, it is also possible to operate either in a neutral medium at a temperature between 0 and 50°C, in one of the solvents mentioned above, or in an acetic medium under conditions identical to those described earlier for the action of a



product of general formula (XXIII) on a product of general formula (XXI).

The products of general formula (XXV) can be prepared by acid hydrolysis of a product of general formula (XXI) to obtain a product of general formula:



followed:

$\alpha$ ) either by the action of a product of general formula:



10 in which X denotes a halogen atom and  $Z'_1$  has the definition given before for  $Z_1$ , except for denoting a chlorine atom

$\beta$ ) or by the action of a product of formula:



15 to obtain a product of general formula (XXV) in which  $Z_1$  denotes a chlorine atom.

The hydrolysis of the product of general formula (XXI) to the product of general formula (XXV) is carried out by means of an aqueous solution of an inorganic acid such as a 0.1 N aqueous solution of hydrochloric acid, the

20

operation being carried out at a temperature in the region of 20°C.

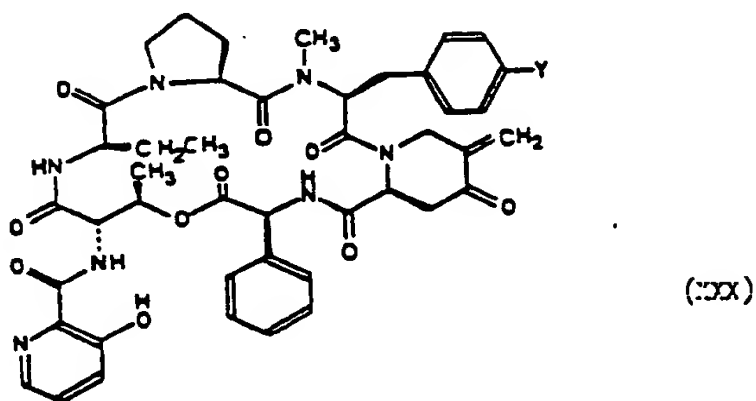
The reaction of the product of general formula (XXVII) with the product of general formula (XXVI) is generally carried out in an organic solvent such as methylene chloride in the presence of an acid-acceptor such as an organic base such as triethylamine, or an inorganic base such as an alkali metal carbonate or bicarbonate, for example sodium or potassium bicarbonate. The operation is generally carried out at a temperature between -20 and +20°C.

The reaction of the product of general formula (XXVIII) with the product of general formula (XXVI) is usually carried out in a chlorinated solvent such as methylene chloride at a temperature between -20 and +20°C.

The products of  
general formula (XIV), in which Y and R<sub>8</sub> are defined as  
above, can be prepared by the action of a thiol of general formula:



5 in which R<sub>8</sub> has the definition given above, on a product of general formula:



in which Y is defined as above.

The reaction is generally performed in an organic  
10 solvent such as an alcohol, e.g. methanol or a chlorinated solvent, e.g. chloroform, or a mixture of these solvents, at a temperature of between -20°C and the refluxing temperature of the reaction mixture, preferably at a temperature in the region of 20°C.

15 It is understood that the thiol of (R) or (S) configuration leads to the synergistin derivative of general formula (XIV) of the corresponding configuration.

The thiol of general formula (XXIX) can be obtained from the thiol ester of general formula:



in which  $R_g$  is defined as above and  $R'$  denotes an alkyl radical containing 1 to 4 carbon atoms, preferably a methyl radical, by any known method for obtaining a thiol from a thiol ester without affecting the remainder of the molecule. The reaction is formed, in particular, by alcoholysis in alkaline medium, e.g. in an alcohol such as methanol, in the presence of sodium methylate or sodium hydroxide, at a temperature of between 20°C and the refluxing temperature of the reaction mixture.

10 The thiol ester of general formula (XXXI) can be prepared by a method similar to that described by R.P. Volante, Tet. Let. 22 (33), 3119 (1981), from an alcohol of general formula:



15 in which  $R_g$  is defined as above, and a thiocarboxylic acid of general formula:



in which  $R'$  is defined as above, by treatment with a mixture of triphenylphosphine and dialkyl azodicarboxylate, e.g. diisopropyl azodicarboxylate.

The reaction is performed under conditions similar to those described in the above reference.

It is understood that the alcohol of general formula (XXXII) of (R) or (S) form leads, respectively, to the thiol ester of general formula (XXXI) of (S) or (R) configuration.

The alcohol of general formula (XXXII) of (R) or (S)

form can be prepared according to the method described by B. Ringdahl et al., Acta. Pharm. Suec., 16, 281 (1979).

The products of general formula (XXX) can be prepared as described in European Patent Publication 133,098.

5        When the products of general formula (XIV) take the form of a mixture of isomers, it is possible to separate the latter by any known method which does not affect the remainder of the molecule; e.g. by high performance liquid chromatography.

10        The new products of general formula (XIV) can be purified by the usual known methods, e.g. crystallization, chromatography or successive extractions in acid and basic medium. For those versed in the art who are familiar with the sensitivity of synergistins in alkaline medium, it is  
15        obvious that "basic medium" is understood to mean a medium which is just sufficiently alkaline to liberate the parent substance from its addition salt with an acid, i.e. a medium in which the pH does not excess 7.5 to 8.

      The new products of general formula (XIV) can be  
20        converted to an addition salt with acids by the action of an acid in an organic solvent such as an alcohol, ketone, ester or chlorinated solvent. The salt precipitates, after concentration of its solution where appropriate; it is separated by filtration or decantation. The addition  
25        salts with acids can also be obtained in the state of aqueous solutions by adding an aqueous solution of the corresponding acid to the product of general formula (XIV).

The products of general formulae (IX), (XV), (XIX), (XXIII) and (XXIV) can be prepared according to, or in a similar manner to, the methods described in the examples below, and especially according to:

- G.G. Urquart et al., Org. Synth., 21, 36 (1941)
- A.I. Vogel, J. Chem. Soc., 1822 (1948)
- J.H. Chapman and L.N. Owen, J. Chem. Soc., 579 (1950)
- H.R. Snyder et al., J. Am. Chem. Soc., 69, 2672 (1947)
- D.D. Reynolds et al., J. Org. Chem., 26, 5125 (1961)
- J.W. Haeffele et al., Proc. Sci. Toilet Goods Assoc., 32, 52 (1959)

- H. Barrer et al., J. Org. Chem., 27, 641 (1962)
- J.H. Biel et al., J. Amer. Chem. Soc., 77, 2250 (1955)

when dealing with a product of general formula (IX), (XIX), (XXIII) or (XXIV) in which  $R_2, R'_6, R''_6$  or  $R'''_6$  denotes a substituted alkylthio or (heterocyclic ring radical)thio radical, or according to:

- A.J.W. Headlee et al., J. Amer. Chem. Soc., 55, 1066 (1933)

B.K. Campbell and K.N. Campbell, J. Amer. Chem. Soc., 60, 1372 (1938)

- R.C. Elderfield et al., J. Amer. Chem. Soc., 68, 1579 (1946)

when dealing with a product of general formula (XXIII) or (XXIV) in which  $R''_6$  or  $R'''_6$  denotes a substituted  
15 alkyloxy or (heterocyclic ring radical)oxy radical, or according to:

- J. Amer. Chem. Soc., 54, 1499 (1932) and
- J. Amer. Chem. Soc., 54, 3441 (1932),

when dealing with a product of general formula (XV) or  
20 of general formula (IX), (XXIII) or (XXIV) in which  $R_2, R''_6$  or  $R'''_6$  are substituted alkylamino radicals, or according to:

E.F. Elslager et al., J. Med. Chem., 17, 99 (1974)

L.M. Werbel et al., J. Het. Chem., 10, 363 (1973)

25 when dealing with a product of general formula (IV), (XXIII) or (XXIV) in which  $R_2, R''_6$  or  $R'''_6$  are (heterocyclic ring radical)amino radicals.

It is to be understood that in the above methods, when  $R_2, R_4, R_5, R'_6, R''_6$  or  $R'''_6$  contain a secondary amine group capable of interfering with the reaction, this must first be protected by any known method which does not affect the remainder of the molecule. The protective  
5 radical is removed after reaction under the conditions described earlier.

Where applicable, the isomers of the products of general formula (I) and/or of the products of general formula (XI) can be separated by chromatography or by high  
10 performance liquid chromatography.

The products of general formula (XI) can be purified as mentioned earlier for the products of general formula (I).

The new products of general formula (XIV) possess the considerable advantage that they can be solubi-  
20 lized in water in the state of salts, at doses which can be used therapeutically, while retaining the general activity spectrum of synergistins. They are active, in particular, on *Staphylococcus aureus* Smith in vitro at concentrations of between 1 and 125 µg/ml and in vivo at doses  
25 of between 5 and 50 mg/kg subcutaneously in mice.

In addition, they are especially advantageous on account of their low toxicity.

The synergistin derivatives of general formula (XIV) have a synergistic effect on the antibacterial action of pristinamycin II<sub>A</sub> on *Staphylococcus aureus* Smith in vitro at doses of between 0.1 and 10 µg/  
15 cm<sup>3</sup> and in vivo in mice at doses of between 10 and 200 mg/kg subcutaneously, when they are combined in proportions varying between 10:90% and 90:10%.

The pristinamycin II<sub>B</sub> derivatives of formula (I) and  
15 their pharmaceutically acceptable salts exhibit particularly advantageous antibacterial properties in vitro and in vivo.

In vitro, the products of formula (I) have shown themselves to be active towards *Staphylococcus aureus* Smith.



In addition, they have a synergistic effect on the antibacterial action of pristinamycin I<sub>A</sub>.

In vivo, the products of formula (I) have shown themselves to be active in the mouse in experimental 5 infections with Staphylococcus aureus Smith by the subcutaneous route. When they are combined with natural or synthetic pristinamycin I<sub>A</sub> in proportions from 10-90% to 90-10%, they have a synergistic effect on the antibacterial action by the subcutaneous route.

10     The ED<sub>50</sub> results are given in Table I which follows. In addition the products of formula (I) are especially advantageous on account of their low toxicity and when n is 2, their non-clastogenicity in vitro.

The products of general formula (I) are more stable 15 in acid conditions than the corresponding 16-oxo-compounds either described in EP 135410 or of general formula (IV).

Compound No.	In vitro concentration µg/ml		In vivo dosage mg/kg s.c.	
	alone	with pristinamycin I <sub>A</sub>	alone	with pristinamycin I <sub>A</sub>
8	30	4	> 100	60
7	-	4	> 100	24
3	-	8	-	32
4	-	8	-	11
9	30	0.5	220	5.5
11	8	2	100	14
5	8	4	50	10
6	30	1	120	9
1	60	1	120	6.5
2	8	2	55	10
12	-	8	70	13
13	-	4	-	10
15	-	8	-	30
<hr/>				
Compound 2/Compound of reference example 62	-	1	-	17
<hr/>				
Compound 1/Compound of reference example 62	-	1	-	7.5

TABLE I

The products of special interest are those of  
10 formula (I) in which the symbol  $R_2$  denotes:

- either a nitrogen-containing 5 or 6-membered heterocyclic ring radical unsubstituted or substituted by an alkyl radical,
- or an alkyl chain of 2 to 4 carbon atoms and substituted  
15 by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, and N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, dialkylamino, dialkylcarbamoyloxy (the alkyl moieties of these two latter radicals being unjoined or joined to form, with the nitrogen atom to which  
20 they are attached, a saturated or unsaturated 5 or 6-membered heterocyclic ring which may contain another hetero-atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl), or substituted by a nitrogen-  
25 containing 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone and

unsubstituted or substituted by alkyl, this heterocyclic ring being linked to the alkyl by a carbon atom of the ring, it being understood that at least one of the substituents carried by the above alkyl chain is a nitrogen-containing substituent capable  
5 of forming salts, and n is 1 or 2;  
and, among these products, those which are especially active are the products of formula (I) in which R denotes an alkyl chain containing 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of  
10 5 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, and dialkylamino (in which the alkyl moieties contain 1 to 3 carbon atoms each or form, with the nitrogen atom to which they are attached, a saturated 5 or 6-membered heterocyclic  
15 ring), or R denotes a nitrogen-containing 5 or 6-membered heterocyclic ring unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the alkyl chain being a nitrogen-containing substituent capable of forming salts, and at least one of  
20 the radicals carried by this chain is placed in a 1- or 2- position, and n is 1 or 2.

For use in therapy, the compounds of formula (I) can be used as such, that is to say in the form of the base, in combination with already known synergists, but, since the chief advantage of the products of the invention is  
10 their solubility in water, it is especially advantageous to use them in the form of pharmaceutically acceptable salts, in combination with known synergists or with the synergists of formula (V), dissolved either in the form of pharmaceutically acceptable salts or, where applicable, in  
15 the form of the base when the solubility is sufficient for the solution produced to contain ( in a volume suitable for a single dose) a quantity of active ingredient which is at least equal to the therapeutically active dose.

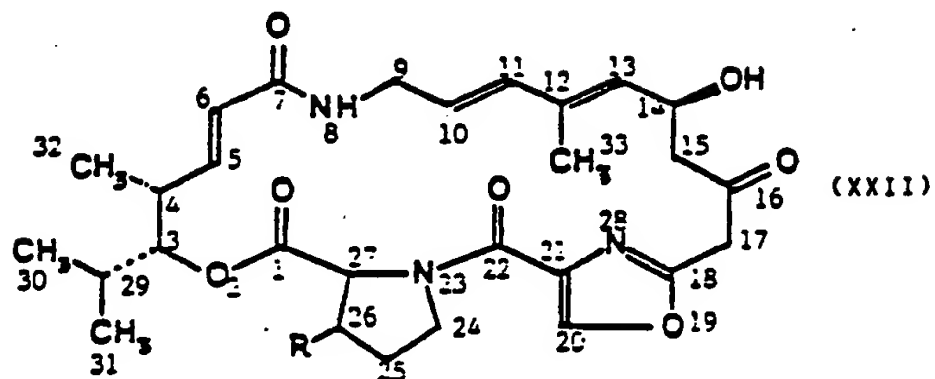
Both for the products of formula (I) and for the  
20 products of formula (V), the pharmaceutically acceptable salts which can be mentioned are the salts of addition with inorganic acids such as hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, or with organic acids, such as acetates, propionates, succinates, maleates,  
25 fumarates, methanesulphonates, p-toluenesulphonates, isethionates, or substitution derivatives of these

compounds. There can also be mentioned, as pharmaceuti-  
cally acceptable salts, the salts with alkali metals (such  
as sodium and potassium salts), with alkaline-earth metals  
(such as the magnesium salt), the ammonium salt and salts  
5 of addition with nitrogen-containing organic bases (etha-  
nolamine, diethanolamine, trimethylamine, triethylamine,  
methylamine, propylamine, diisopropylamine, N,N-dimethyl-  
ethanolamine, benzylamine, dibenzylamine, dicyclohexyl-  
benzylamine, N-benzyl- $\beta$ -phenethylamine, N,N'-dibenzyl-  
10 ethylenediamine, benzhydramine, arginine, leucine,  
lysine or N-methylglucamine).

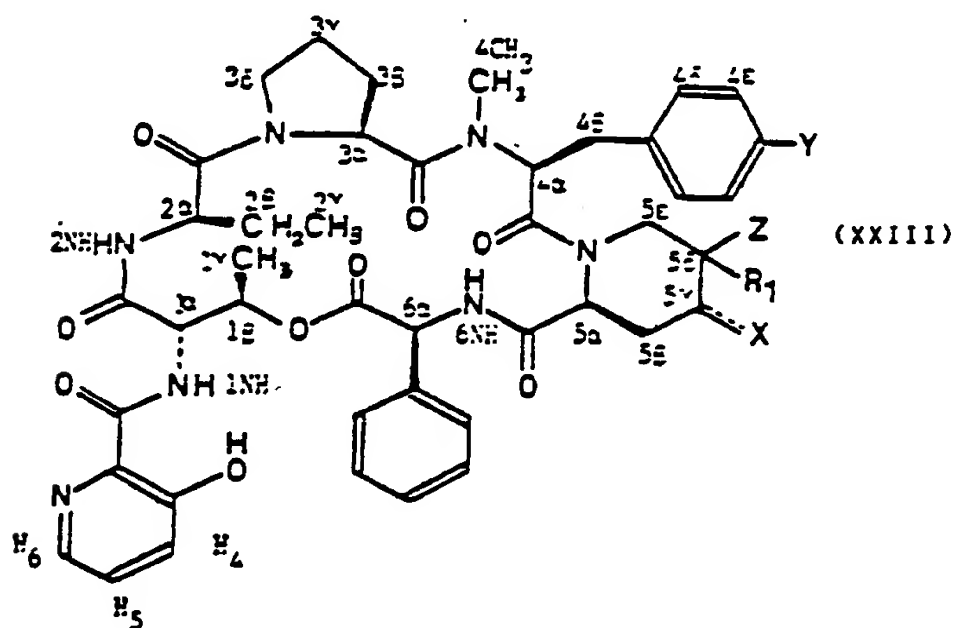
Quaternary ammonium salts corresponding to the  
anions listed above can be mentioned as pharmaceutically  
acceptable salts for the products of general formula (V)  
15 in which Z denotes a radical of general formula (VII) in  
which R<sub>4</sub> denotes a trialkylammonio radical.

The following examples, given without implying  
any limitation, show how the invention can be put into  
practice. The NMR spectra of the products illustrated in  
20 these examples and in the reference examples which follow,  
show general characteristics which are common to all the  
products of general formula (I) or of general formula (V)  
and individual characteristics which are specific to each  
of the products, depending on the substituents. Only the  
25 individual characteristics due to the changeable radicals  
are mentioned in the examples or reference examples which  
follow. For the products of general formula (I), all the

protons are designated according to the numbering indicated in the following formula:



For the synergistins of general formula (V) all the 5 protons are designated according to the numbering indicated in the general formula (XXIII); this numbering is that recommended by J.O. Anteunis et al., [Eur. J. Biochem., 58, 259 (1975)].



Unless stated otherwise, all the spectra were recorded at 250 MHz in deuteriochloroform; the chemical shifts are expressed in ppm relative to the tetramethylsilane signal. The abbreviations used in the following

5 text are as follows:

s = singlet

d = doublet

t = triplet

mt = multiplet

10 m = unresolved bands

dd = doublet of doublets

dt = doublet of triplets

ddd = doublet of doublets of doublets

dddd = doublet of doublets of doublets of doublets

15 It is to be understood that the various isomers have been classified arbitrarily according to the chemical shifts observed in NMR.

The names isomer A<sub>1</sub> and isomer A<sub>2</sub> of the products of general formula (I) in which n = 1 are given to the isomers which have the characteristics:

approximately 1.7 (s, -CH<sub>3</sub> at 33); approximately 3.8 (s,

>CH<sub>2</sub> at 17); < 5 (d, -H<sub>27</sub>) isomer A<sub>2</sub> or > 5 (d,

-H<sub>27</sub>) isomer A<sub>1</sub>; approximately 5.50 (broad d, -H<sub>13</sub>);

approximately 6.20 (d, -H<sub>11</sub>); approximately 6.6 (>NH

25 at 8); ≥ 8 (s, -H<sub>20</sub>).

The names isomer B<sub>1</sub> and isomer B<sub>2</sub> of the products of general formula (I) in which n = 1 are given to



the isomers which have the characteristics:  
approximately 1.5 (s, -CH<sub>3</sub> at 33); approximately 3.7 and  
3.9 (2d, >CH<sub>2</sub> at 17); approximately 4.8 (mt, -H<sub>13</sub>);  
< 5 (d, -H<sub>27</sub>) isomer B<sub>2</sub> or > 5 (d, -H<sub>27</sub>). isomer B<sub>1</sub>;  
5 approximately 5.70 (borderline AB, -H<sub>11</sub> and -H<sub>10</sub>); approxi-  
mately 7.7 (>NH at 8); approximately 7.8 (s, -H<sub>20</sub>).

The name isomer A of the product of general for-  
mula (VII) is given to the isomer which has NMR characteris-  
tics identical to those listed above for the isomers A<sub>1</sub>  
10 and A<sub>2</sub> of the products of general formula (I), it being  
understood that the H at 27 is characterized by: 4.7 (d,  
J ≤ 1 Hz).

The name isomer B of the product of general formula  
(VII) is given to the isomer which has NMR characteristics  
15 identical to those listed above for the isomers B<sub>1</sub> and  
B<sub>2</sub> of the products of general formula (I), it being  
understood that the H at 27 is characterized by: 4.6 (d,  
J ≥ 2.5 Hz).

In the following examples, the name "flash" chroma-  
20 tography is given to a purification technique in which a  
short chromatography column is used and operated under an  
intermediate pressure (50 kPa) with the use of a silica  
with a particle size distribution of 40-53 μm, according to  
W.C. Still, M. Kahn and A. Mitra (J. Org. Chem. 43, 2923  
25 (1978)).

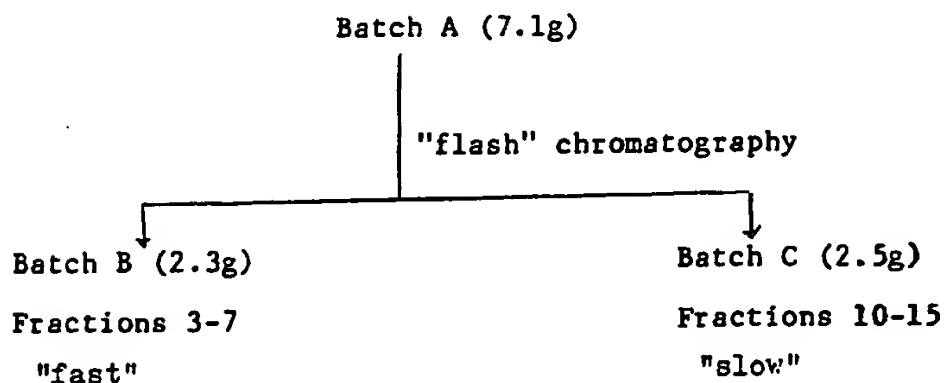
In the examples described below, unless stated  
otherwise, all the products can be dissolved at a strength  
of at least 2%, in the form of hydrochloride.

EXAMPLE 1

Compounds 1 and 2

To a stirred solution of 26-(2-diethylaminoethyl)-  
sulphonylpristinamycin II<sub>B</sub> (isomer A) (7.9g) in  
5 methanol (250 cc) at room temperature was added  
portionwise sodium borohydride (0.47g) over 5 minutes.  
After stirring at room temperature for 20 minutes  
dichloromethane (250 cc) and water (330 cc) were added  
and the organic phase separated. The aqueous phase was  
10 extracted with a further 100 cc of dichloromethane, the  
combined organic phases were dried over anhydrous  
magnesium sulphate and evaporated to dryness affording  
a light yellow solid (7.1g). Partial purification by  
"flash" chromatography on silica was carried out  
15 [eluent: chloroform-methanol (90-10 by volume)] 100 cc  
fractions being collected, according to the following  
scheme:

Purification Scheme



Batch B was combined with a similar batch ( $B^1$ , 0.6g) [and batch C was combined with a similar batch ( $C^1$ , 1.0g)], produced from treating 3.3g of 26-(2-diethylaminoethyl)sulphonylpristinamycin  $II_B$  (isomer A) with sodium borohydride according to the conditions above.

Further purification of the combined batches  $B+B^1$  by "flash" chromatography on silica [eluent: ethyl acetate-methanol (90-10 by volume)] 30 cc fractions being collected, was carried out. After concentrating fractions 34 to 39 to dryness under reduced pressure at 40-45°C, dissolving the residue (0.66g) in ethyl acetate (6 cc) and pouring the solution into light petroleum (bp 40-60°C) (70 cc), 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16 $\alpha$ -hydroxypristinamycin  $II_B$  (isomer A) ("fast" 16-stereoisomer) was obtained as a colourless solid (0.55g) melting slowly above 104°C. Found: C, 58.4; H, 7.6; N, 7.7; S, 4.47%. Calculated for  $C_{34}H_{52}N_4O_9S$ : C, 58.9; H, 7.6; N, 8.1; S, 4.63%.

Further purification of the combined batches  $C+C^1$  by "flash" chromatography on silica [eluent: ethyl acetate-methanol (85-15 by volume)] 30 cc fractions being collected, was carried out. After concentrating fractions 31 to 39 to dryness under reduced pressure at

40-45°C, dissolving the residue (1.0g) in ethyl acetate (7 cc) and pouring the solution into light petroleum (bp 40-60°C) (75 cc), 16-deoxy-26-(2-diethylaminoethyl)-sulphonyl-16beta-hydroxypristinamycin II<sub>B</sub> hydrate

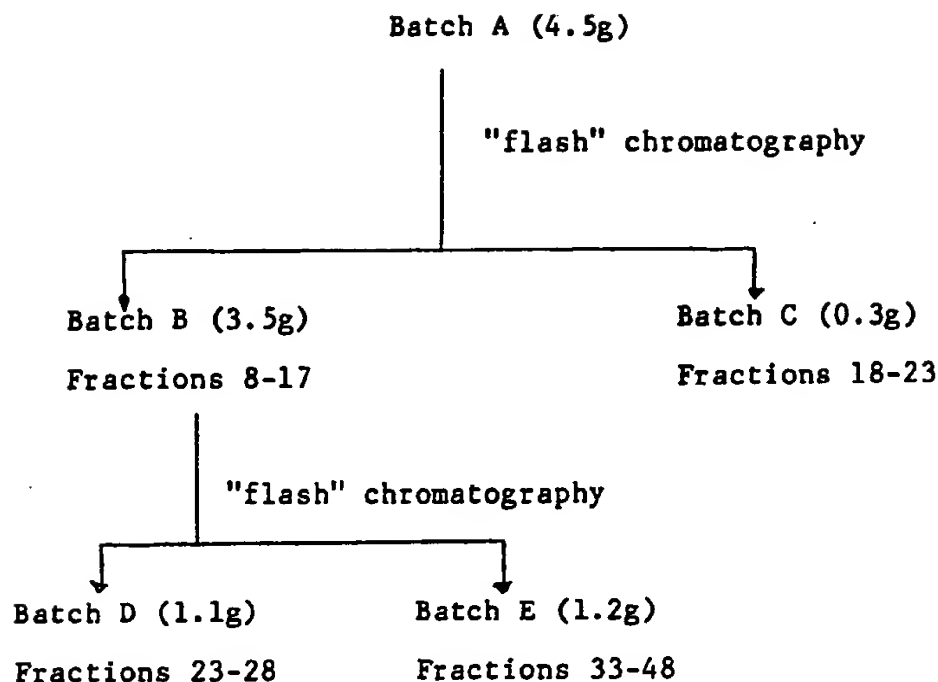
- 5 (isomer A) ("slow" 16-stereoisomer) was obtained as a colourless solid (0.66g) melting slowly above 106°C. Found: C, 57.7; H, 7.4; N, 7.8; S, 4.53%. Calculated for  $C_{34}H_{52}N_4O_9S \cdot H_2O$ : C, 57.4; H, 7.67; N, 7.88; S, 4.51%.

EXAMPLE 2

Compounds 3 and 4

To a stirred solution of 26-(2-diisopropylamino-ethyl)thiopristinamycin II<sub>B</sub> (isomer A) (4.0g) in methanol (80 cc) at room temperature was added dropwise  
5 over 15 minutes a solution of sodium borohydride (0.296g) in water (6 cc), whilst maintaining the reaction temperature at 25°C with external cooling. The resulting clear solution was stirred for a further 75 minutes at room temperature then poured into water  
10 (700 cc) and the pH of the solution adjusted to 4 by addition of dilute hydrochloric acid (1M). The pH of the solution was then adjusted to 8 by addition of dilute sodium hydroxide solution (1M) and extracted twice with chloroform (total 400 cc). The aqueous  
15 phase was saturated with sodium chloride and further extracted with ethyl acetate (500 cc). The combined chloroform and ethyl acetate extracts were dried over anhydrous magnesium sulphate and evaporated affording a colourless syrup (4.5g). Two successive purifications  
20 by "flash" chromatography on silica were carried out [eluent: chloroform-methanol (90-10 by volume)] 50 cc fractions being collected, according to the following scheme:

Purification Scheme



In all cases, the fractions recovered were concentrated to dryness under reduced pressure at 40-45°C.

- 5 Batch D was dissolved in ethyl acetate (30 cc), the solution was filtered and poured into hexane (120 cc) affording 16-deoxy-26-(2-diisopropylaminoethyl)thio-16 $\alpha$ -hydroxypristinamycin II<sub>B</sub> hydrate (isomer A) ("fast" 16-stereoisomer) as a white powder (0.83g)
- 10 melting slowly above 115°C. Found: C, 60.4; H, 8.0; N, 7.8; S, 4.58; H<sub>2</sub>O, 2.55%. Calculated for C<sub>36</sub>H<sub>56</sub>N<sub>4</sub>O<sub>7</sub>S.H<sub>2</sub>O:  
C, 61.2, H, 8.27; N, 7.93; S, 4.54; H<sub>2</sub>O, 2.55%.

Batches C and E were combined, dissolved in ethyl acetate (35 cc), the solution was filtered and poured into hexane (150 cc) affording  
16-deoxy-26-(2-diisopropylaminoethyl)thio-16 $\beta$ -hydroxy  
5 pristinamycin II<sub>B</sub> hydrate (isomer A) ("slow"  
16-stereoisomer) as a white powder (0.92g) melting  
slowly above 120°C. Found: C, 60.8; H, 7.9; N, 7.8;  
S, 4.56; H<sub>2</sub>O, 2.7%; Calculated for  
C<sub>36</sub>H<sub>56</sub>N<sub>4</sub>O<sub>7</sub>S.H<sub>2</sub>O: C, 61.2; H, 8.27; N, 7.93;  
10 S, 4.54; H<sub>2</sub>O, 2.55%.

EXAMPLE 3

Compounds 5 and 6

To a stirred solution of 26-(2-diisopropylamino-ethyl)sulphonylpristinamycin II<sub>B</sub> (isomer A<sub>2</sub>) (4.0g)  
5 in methanol (100 cc) at room temperature was added portionwise sodium borohydride (0.4g) over 10 minutes, whilst maintaining the reaction temperature at 25°C with external cooling. The resulting clear solution was stirred for a further 75 minutes at room  
10 temperature then poured into water (750 cc). Glacial acetic acid (5 cc) was added to adjust the pH of the solution to 4, followed by addition of solid sodium bicarbonate to bring the pH to 7.5. The mixture was extracted with ethyl acetate (2x250 cc), the extracts  
15 were dried over anhydrous magnesium sulphate and evaporated yielding a golden meringue (3.5g), which was purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume, followed by 80-20 by volume) 50 cc fractions being collected. Fractions  
20 17 to 24 were combined and concentrated to dryness under reduced pressure at 40-45°C to give a white solid (0.9g) which was dissolved in ethyl acetate (20 cc). After filtering the solution, hexane (100 cc) was added and the precipitate separated off by filtration to give



16-d oxy-26-(2-diisopropylamino thyl)sulphinyl-16alpha-hydroxypristinamycin II<sub>B</sub> hydrate (isomer A<sub>2</sub>) ("fast" 16-stereoisomer) as a white powder (0.55g) melting slowly above 120°C.

- 5 Fractions 31 to 40 were combined and concentrated to dryness under reduced pressure at 40-45°C to give a white solid (1.3g) which was dissolved in ethyl acetate (20 cc). After filtering the solution, hexane (100 cc) was added and the precipitate separated off by
- 10 filtration to give 16-deoxy-26-(2-diisopropylamino-ethyl)sulphinyl-16beta-hydroxypristinamycin II<sub>B</sub> hydrate (isomer A<sub>2</sub>) ("slow" 16-stereoisomer) as a white powder (0.7g) melting slowly above 120°C. Found: C, 59.0; H, 7.6; N, 7.5; S, 3.9; H<sub>2</sub>O, 3.1%:
- 15 Calculated for C<sub>36</sub>H<sub>56</sub>N<sub>4</sub>O<sub>8</sub>S.1.5 H<sub>2</sub>O: C, 59.1; H, 8.13; N, 7.7; S, 4.4; H<sub>2</sub>O, 3.7%.

EXAMPLE 4

Compound 7

To a stirred solution of 2-diethylaminoethanethiol hydrochloride (0.65g) in methanol (40 cc) under  
5 nitrogen was added sodium methoxide (0.21g) portionwise followed by 16-deoxy-16beta-hydroxypristinamycin II<sub>A</sub> ("slow" 16-stereoisomer) (2g). The pale yellow solution was kept at room temperature for 18 hours, evaporated to low volume and absorbed onto silica then  
10 purified by "flash" chromatography on silica [eluent: chloroform-methanol (90-10 by volume)] 40 cc fractions being collected. Fractions 8 to 15 were combined and concentrated to dryness under reduced pressure at 40-45°C. The residue (1.23g) was further purified by  
15 "flash" chromatography on silica [eluent: methanol] 7 cc fractions being collected. Fractions 18 to 36 were combined and concentrated to dryness under reduced pressure at 40-45°C to give a white solid (0.73g) which was dissolved in ethyl acetate (7 cc). The solution  
20 was poured into light petroleum (b.p. 40-60°C) (75 cc) affording 16-deoxy-26-(2-diethylaminoethyl)thio-16beta-hydroxypristinamycin II<sub>B</sub> hemihydrate (isomer A) as a white powder (0.6g) melting slowly above 105°C to give a complete melt at 125°C. Found:  
25 C, 60.6; H, 8.0; N, 8.2; S, 4.66; H<sub>2</sub>O, 1.4%.  
Calculated for C<sub>34</sub>H<sub>52</sub>N<sub>4</sub>O<sub>7</sub>S.0.5H<sub>2</sub>O: C, 60.9; H, 7.98; N, 8.36; S, 4.79; H<sub>2</sub>O, 1.34%.

EXAMPLE 5

Compound 8

To a stirred solution of 16-deoxy-16alpha-hydroxy-pristinamycin II<sub>A</sub> ("fast" 16-stereoisomer) (1.54g) in  
5 methanol (40 cc) under argon at 0°C was added  
2-diethylaminoethanethiol hydrochloride (0.501g)  
followed by sodium methoxide (0.162g) portionwise. The  
resulting pale yellow solution was kept at 5°C for 42  
hours, evaporated to 5 cc volume and purified by  
10 "flash" chromatography on silica (eluent: methanol)  
13 cc fractions being collected. Fractions 12 to 17  
were combined and concentrated to dryness under reduced  
pressure at 40-45°C to give a white solid (1.2g) which  
was dissolved in ethyl acetate (3 cc). The solution  
15 was poured into light petroleum (b.p. 40-60°C) (10 cc)  
affording  
16-deoxy-26-(2-diethylaminoethyl)thio-16alpha-hydroxy-  
pristinamycin II<sub>B</sub> (isomer A) as a white powder (1.0g)  
melting slowly above 112°C to give a complete melt  
20 122-125°C. Found: C, 61.4; H, 8.0; N, 8.2; S, 4.56%.  
Calculated for C<sub>34</sub>H<sub>52</sub>N<sub>4</sub>O<sub>7</sub>S: C, 61.8; H, 7.93;  
N, 8.48; S, 4.85%.

EXAMPLE 6

Compounds 9, 10 and 11

To a stirred solution of 16-deoxy-26-(2-diethyl-  
aminoethyl)thio-16alpha-hydroxypristinamycin II<sub>B</sub>  
5 (isomer A) ("fast" 16-stereoisomer) (3.4g) in  
dichloromethane (250 cc) at 5°C was added trifluoro-  
acetic acid (0.594g) followed by 3-chloroperbenzoic  
acid (0.892g). After stirring at 5°C for 18 hours the  
reaction mixture was evaporated under reduced pressure  
10 at 40-45°C. The residue was purified by "flash"  
chromatography on silica [eluent: chloroform- methanol  
(87-13 by volume)] 20 cc fractions being collected.  
Fractions 26 to 34 were concentrated to dryness under  
reduced pressure at 40-45°C and the residue further  
15 purified by "flash" chromatography as above. Fractions  
10 to 16 afforded after concentration to dryness under  
reduced pressure at 40-45°C  
16-deoxy-26-(2-diethylaminoethyl)sulphinyl-  
16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>)  
20 ("fast" 16-stereoisomer) as a white powder (0.6g)  
m.p. 138-140°C. Found: C, 57.4; H, 7.3; N, 7.6;  
S, 4.61; Cl, 3.61; H<sub>2</sub>O, 1.62%. Calculated for  
C<sub>34</sub>H<sub>52</sub>N<sub>4</sub>O<sub>8</sub>S. 0.6H<sub>2</sub>O. 0.25 CHCl<sub>3</sub>: C, 57.3;  
H, 7.51; N, 7.81; S, 4.47; Cl, 3.71; H<sub>2</sub>O, 1.51%.

Fractions 36 to 46 from the first purification step were concentrated to dryness under reduced pressure at 40-45°C affording 16-deoxy-26-(2-diethylaminoethyl)-sulphinyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomers  
5 A<sub>1</sub> + A<sub>2</sub>) ("fast" 16-stereoisomer) as a white solid (0.5g), m.p. 138-140°C. Found: C, 57.7; H, 7.4; N, 7.7; S, 4.52; Cl, 3.10; H<sub>2</sub>O, 1.13%. Calculated for C<sub>34</sub>H<sub>52</sub>N<sub>4</sub>O<sub>8</sub>S. 0.45H<sub>2</sub>O.0.22 CHCl<sub>3</sub>: C, 57.4; H, 7.73; N, 7.88; S, 4.51; Cl 3.3; H<sub>2</sub>O, 1.14%.

10 By proceeding in a similar manner but using the isomeric Compound 7 prepared in Example 4 there was prepared 16-deoxy-26-(2-diethylaminoethyl)sulphinyl-16beta-hydroxypristinamycin (isomer A<sub>2</sub>).

EXAMPLE 7

Compounds 12 and 13

To a solution of 16-deoxy-16beta-hydroxy  
pristinamycin II<sub>A</sub> ("slow" 16-stereoisomer) (1.05g) in  
5 ethanol (15 cc) was added ethylamine (5 cc of a 33% w/w  
solution in ethanol), kept at room temperature for 90  
hours and then evaporated to dryness. The resultant  
pale brown solid was purified by "flash" chromatography  
on silica [eluent: chloroform-methanol (90-10 by  
10 volume)]. The second component eluted, after  
concentration to dryness under reduced pressure at  
40-45°C, was dissolved in ethyl acetate. Addition of  
light petroleum (b.p. 40-60°C), followed by filtration,  
gave 16-deoxy-26-ethylamino-16beta-hydroxypristinamycin  
15 II<sub>B</sub> hydrate (isomer A) as a white powder (0.46g),  
m.p. 135-137°C. Found: C, 60.6; H, 7.5; N, 9.4; H<sub>2</sub>O,  
2.1%. Calculated for C<sub>30</sub>H<sub>44</sub>N<sub>4</sub>O<sub>7</sub> · 0.9H<sub>2</sub>O: C, 61.18;  
H, 7.84; N, 9.51; H<sub>2</sub>O, 2.75%.

By proceeding in a similar manner but using the  
20 isomeric 16-deoxy-16alpha-hydroxypristinamycin II<sub>A</sub>  
(0.92g), the isomeric 16-deoxy-26-ethylamino-16alpha-  
hydroxypristinamycin II<sub>B</sub> hydrate (isomer A) was  
obtained as a white powder (0.5g) m.p. 131-134°C.  
Found: C, 62.8; H, 7.9; N, 9.7; H<sub>2</sub>O, 1.5%.  
25 Calculated for C<sub>30</sub>H<sub>44</sub>N<sub>4</sub>O<sub>7</sub> · 0.25H<sub>2</sub>O: C, 62.4; H, 7.77;  
N, 9.71; H<sub>2</sub>O, 0.78%.

EXAMPLE 8

Compounds 14 and 15

To a solution of 16-deoxy-16alpha-hydroxy-pristinamycin II<sub>A</sub> ("fast" 16-stereoisomer) (1.5g) in  
5 ethanol (60 cc) was added 2-diethylaminoethylamine (1 cc) and the mixture was stirred at room temperature for 30 hours. After evaporating to dryness under reduced pressure at 40-45°C the residual brown solid was purified by "flash" chromatography on silica  
10 [eluent: ethyl acetate-methanol (92-8 by volume)] 35 cc fractions being collected. Fractions 15-45 were combined and evaporated to dryness under reduced pressure at 40-45°C affording a white solid (0.45g). This material was combined with a second batch prepared  
15 from reacting 1.6g 16-deoxy-16alpha-hydroxy-pristinamycin II<sub>A</sub> ("fast" 16-stereoisomer) in ethanol (70 cc) with 2-diethylaminoethylamine (1.08 cc) as above. The combined batches were further purified by "flash" chromatography on silica [eluent: ethyl  
20 acetate-methanol (98-2 by volume)] 30 cc fractions being collected. Fractions 31-59 were combined and concentrated to dryness under reduced pressure at 40-45°C to give a white solid (0.8g) which was dissolved in ethyl acetate. The solution was filtered

and light petroleum (b.p. 40-60°C) was added. On cooling 16-deoxy-26-(2-diethylaminoethyl)amino-16alpha-hydroxypristinamycin II<sub>B</sub> hemihydrate was obtained as white crystals (0.7g) m.p. 118-120°C. Found: C, 62.1;

5 H, 8.4; N, 10.3; H<sub>2</sub>O, 1.3%. Calculated for C<sub>34</sub>H<sub>53</sub>N<sub>5</sub>O<sub>7</sub>·0.5H<sub>2</sub>O: C, 62.6; H, 8.3; N, 10.7; H<sub>2</sub>O, 1.4%.

By proceeding in a similar method but using the isomeric 16-deoxy-16beta-hydroxypristinamycin II<sub>A</sub> (1.4g), the isomeric 16-deoxy-26-(2-diethyl-  
10 aminoethyl)amino-16-beta-hydroxypristinamycin II<sub>B</sub> hydrate was obtained as white crystals (0.49g) m.p. 123-125°C. Found: C, 59.5; H, 8.0; N, 10.0%. Calculated for C<sub>34</sub>H<sub>53</sub>N<sub>5</sub>O<sub>7</sub>·2.5H<sub>2</sub>O: C, 59.3; H, 8.5; N, 10.2%.



EXAMPLE 2

By using the same method as that described in Example 2 of European Patent Publication No. 191662, but starting from 26-(2-cyclopentylaminoethyl)-  
5 thiopristinamycin II<sub>B</sub> (isomer A)(2.9 g), sodium bicarbonate (0.72 g), and 98% meta-chloroperbenzoic acid (0.75 g) at -30°C, and after purification by "flash" chromatography [eluent : dichloromethane-methanol (90-10 by volume)], 30 cc fractions being  
10 collected, and concentrating fractions 25 to 31 to dryness under reduced pressure (2.7 kPa) at 30°C, a yellow solid (0.7 g) is obtained which is re-purified by "flash" chromatography [eluent : dichloromethane-methanol (95 - 5 by volume)], 20 cc fractions being  
15 collected. After concentrating fractions 78 to 95 to dryness under reduced pressure (2.7 kPa) at 30°C, 26-(2-cyclopentylaminoethyl)sulphonylpristinamycin II<sub>B</sub> (isomer A<sub>2</sub>)(2.3 g) is obtained in the form of a pale yellow solid melting at about 114°C.

20

NMR spectrum

1.30 to 2.25 (mt,  $\text{CH}_2$  of cyclopentyl)

1.76 (s, -CH<sub>3</sub> at 33)

2.80 (mt, -H<sub>4</sub>)

2.85 to 3.25 (mt,  $-\text{S}-\underset{\text{O}}{\text{CH}_2}-\text{CH}_2-\text{N}-\overset{\text{CH}}{\text{CH}_2}$  ;  $\text{CH}_2$  at 15; -H<sub>26</sub>)

25

3.82 (s,  $\text{CH}_2$  at 17)

4.81 (d, -H<sub>27</sub>)

5.53 (d,  $-H_{13}$ )

6.19 (d,  $-H_{11}$ )

6.30 (mt,  $>NH$  at 8)

8.15 (s,  $-H_{20}$ )

- 5        26-(2-cyclopentylaminoethyl)thiopristinamycin II<sub>B</sub>  
(isomer A) can be prepared by using the same procedure  
as that described in Example 2 of European Patent  
Publication No. 191662, but starting from pristinamycin  
II<sub>A</sub> (15 g) and 2-cyclopentylamino-ethanethiol (4.3  
10 g). After stirring for 3 days at  $-20^{\circ}C$  and  
purification by "flash" chromatography [eluent :  
dichloromethane-methanol (90-10 by volume)], 30 cc  
fractions being collected, followed by concentration of  
fractions 69 to 92 to dryness under reduced pressure  
15 (2.7 kPa) at  $30^{\circ}C$ , a yellow solid (5.2 g) is obtained,  
which is dissolved in a mixture of acetone (45 cc) and  
diethyl ether (90 cc). The precipitate which forms is  
separated by filtration and then dried under reduced  
pressure (90 Pa) at  $35^{\circ}C$  to give  
20 26-(2-cyclopentylaminoethyl)thiopristinamycin II<sub>B</sub>  
(isomer A) (2.9 g) in the form of a pale yellow solid  
melting at about  $144^{\circ}C$ .

NMR spectrum:

- 1.50 to 2 (mt,  $>CH_2$  of cyclopentyl)  
25 1.73 (s,  $-CH_3$  at 33)  
2.78 (mt,  $-H_4$ )  
2.85 to 3.05 (mt,  $-S-CH_2-CH_2N'$ )

2.88 and 3.18 (2d,  $\text{CH}_2$  at 15)

3.26 (mt,  $\text{N-CH}$ )

3.42 (mt,  $-\text{H}_{26}$ )

3.82 (s,  $\text{CH}_2$  at 17)

5 4.70 (d,  $-\text{H}_{27}$ )

5.48 (d,  $-\text{H}_{13}$ )

6.18 (d,  $-\text{H}_{11}$ )

6.82 (mt,  $\text{NH}$  at 8)

8.15 (s,  $-\text{H}_{20}$ )

10 2-cyclopentylaminoethanethiol can be obtained by a  
method similar to that described by D.D. Reynolds et  
al., J.Org.Chem. 26, 5109 (1961).

15

20

25

REFERENCE EXAMPLE 1

3-Mercaptoquinuclidine (2.8 g) is added to a solution of 56-methylenepristinamycin 1A (4.4 g) in a mixture of methanol (40 cc) and chloroform (20 cc), and the solution obtained is then stirred for 44 hours at a temperature in the region of 20°C. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is suspended in ethyl ether (100 cc) and then separated by filtration. The solid thereby obtained is washed with ethyl ether (3 x 10 cc) and then purified by flash chromatography [eluant: methylene chloride/methanol (90:10 by volume)], collecting 100-cc fractions. The fractions 11 to 35 are combined and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is stirred in ethyl ether (120 cc). The solid obtained is separated by filtration and then purified again by flash chromatography [eluant: methylene chloride/methanol (85:15 by volume)], collecting 100-cc fractions. Fractions 3 to 7 are combined and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue is stirred in

ethyl ether (50 cc) and the solid thereby obtained separated by filtration, washed with ethyl ether (3 x 5 cc) and then dried under reduced pressure (27 Pa) at 20°C. 5δ-[(3-quinuclidinyl)thiomethyl]pristinamycin IA (1.7 g) is thereby obtained in the form of a pale yellow solid, m.p. about 200°C.

NMR spectrum

Mixture of 4 isomers

2.88 and 2.89 (2s, 4 -N(CH<sub>3</sub>)<sub>2</sub>)

10 3.21 and 3.22 (2s, 4 -CH<sub>3</sub>)

6.51 and 6.53 (2d, 2 -NH-)

6.57 and 6.58 (2d, 4ε)

7.82 and 7.85 (m, the H<sub>6</sub> of the 2 preponderant isomers)

15 7.95 (m, the H<sub>6</sub> of the 2 minority isomers)

8.78 and 8.81 (2d, 6 -NH- of 2 preponderant isomers)

8.98 and 9.0 (2d, 6 -NH- of the 2 minority isomers)

A 5 % strength aqueous solution of 5δ-[(3-quinuclidinyl)thiomethyl]pristinamycin IA is obtained with:

20 product ..... 100 mg

0.1N hydrochloric acid.. 0.98 cc

distilled water .....qs 2 cc

3-Mercaptoquinuclidine may be prepared in the

following manner:

25 Sodium methylate (0.5 g) is added to a solution of 3-(acetylthio)quinuclidine (14.5 g) in methanol (150 cc). The reaction mixture is then heated under reflux for

1 hour. Sodium methylate (0.5 g) is added again and the mixture is then heated under reflux for 2 hours. The reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. Distilled water (40 cc) is added to the residue obtained, followed by acetic acid (approximately 1 cc) to obtain a pH in the region of 8. The mixture obtained is extracted with methylene chloride (3 x 20 cc). The combined organic phases are dried over sodium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The brown oil obtained is distilled under reduced pressure (920 Pa); the fraction distilling at about 94°C is collected. 3-Mercaptoquinuclidine (2.8 g) is thereby obtained.

3-(Acetylthio)quinuclidine may be obtained in the following manner:

Diisopropyl azodicarboxylate (31.6 cc) is added dropwise in the course of 30 minutes to a solution, maintained at 5°C under an atmosphere of nitrogen, of triphenylphosphine (42 g) in tetrahydrofuran (300 cc). The suspension obtained is then stirred for 30 minutes at 5°C. A solution of 3-hydroxyquinuclidine (10.2 g) and thiolacetic acid (11.4 cc) in tetrahydrofuran (600 cc) is then added to this suspension, maintained at 5°C, in the course of 30 minutes. The reaction mixture is then stirred for 20 hours at a temperature in the region of 20°C. It is then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. The oil obtained is dissolved in

ethyl ether (400 cc), and then washed with hydrochloric acid (3 x 160 cc). The combined aqueous phases are washed with ethyl ether (100 cc) and then neutralized to a pH in the region of 7 by adding sodium bicarbonate. The pH of the solution obtained is then adjusted to about 9 by adding a few drops of 10N aqueous sodium hydroxide solution. The mixture is extracted with methylene chloride (3 x 200 cc). The combined organic phases are dried over sodium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. 3-(Acetylthio)quinuclidine (14.7 g) is thereby obtained in the form of a brown oil [Rf = 0.33; eluant: methylene chloride/methanol (90:10 by volume)].

REFERENCE EXAMPLE 2

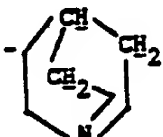
Working in a manner similar to that described in Ref. Ex.1, but starting with 5 $\delta$ -methylenepristinamycin 1A (6.15 g) and (3S)-3-mercaptoquinuclidine (1.1 g) and after two purifications by flash chromatography, collecting 50-cc fractions [1st flash chromatography: eluant: methylene chloride/methanol (90:10 by volume), concentration to dryness of the fractions 12 to 36; 2nd flash chromatography: eluant: methylene chloride/methanol (90:10 by volume), concentration to dryness of the fractions 3 to 20], 5 $\delta$ -{[(3S)-3-quinuclidinyl]thiomethyl}pristinamycin 1A (2.6 g) is obtained in the form of a pale yellow powder. This product may be obtained in the crystallized state in the following manner:

56-[[[(3S)-3-quinuclidinyl]thiomethyl]pristinamycin 1A (2.6 g) is dissolved in methanol (20 cc). A yellow solution is obtained. After filtration and drying under reduced pressure (27 Pa) at 30°C, a crystalline precipitate appears after priming by scratching. 56-[[[(3S)-3-quinuclidinyl]thiomethyl]pristinamycin 1A (1.2 g) is obtained in the form of white crystals, m.p. about 200°C (product crystallized in combination with methanol).


NMR spectrum; 1 isomer (traces of the isomer in respect of the 56 carbon)

10.

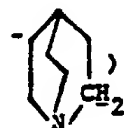
0.62 (dd,  $J = 15$  and  $6$ , 1H, 5B<sub>2</sub>)

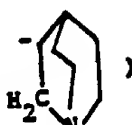
1.6 to 2.30 (m, 6H,  and 56)

2.4 (d,  $J = 15$ , 1H, 5B<sub>1</sub>)

2.5 to 2.75 (m, 5E<sub>2</sub>, 1H of  and 1H of -CH<sub>2</sub>S-)

15

2.9 to 3.20 (m, -S-CH<, 1H of -CH<sub>2</sub>S- and )

3.30 (m, 1H of )

4.98 (dd,  $J = 14$  and  $7.5$ , 1H, 5E<sub>1</sub>)

5.30 (m, 2H, 5a and 4a)

7.90 (dd, 1H, the H<sub>6</sub>)

20

56-[[[(3S)-3-quinuclidinyl]thiomethyl]pristinamycin 1A may also be crystallized in the following manner:  
56-[[[(3S)-3-quinuclidinyl]thiomethyl]pristina-



mycin 1A (17.4 g) is dissolved in acetone (87 cc) which has been brought to reflux beforehand. The solution obtained is filtered and the insoluble material is rinsed with acetone (10 cc). After 3 hours at 20°C, the crystals  
5 obtained are filtered and then dried. Recrystallization of the product (14.8 g) obtained in acetone (75 cc) under the same conditions gives, after filtration followed by drying under reduced pressure (90 Pa) at 20°C, white crystals (12.2 g), m.p. about 185-190°C.

10 (3S)-3-Mercaptoquinuclidine may be obtained in the following manner:

10N aqueous sodium hydroxide solution (30 cc) is added slowly to a solution of (3S)-3-(acetylthio)quinu-  
clidine (29 g) in methanol (30 cc) maintained at approxi-  
15 mately 25°C. The reaction mixture is stirred for 2 hours at a temperature in the region of 20°C. The pH of the reaction mixture is then brought to a value in the region of 9 by adding acetic acid (approximately 10 cc). The mixture obtained is extracted with methylene chloride  
20 (3 x 100 cc). The combined organic phases are dried over sodium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The residue obtained is purified by distillation under reduced pressure (970 Pa). (3S)-3-Mercaptoquinuclidine (12 g) is  
25 thereby obtained in the form of white crystals which melt at 46°C and distil at 95°C under 970 Pa ( $\alpha_D^{20} = -118^\circ$ ,  $c = 1.1$ , methanol).

(3S)-3-(Acetylthio)quinuclidine may be obtained in a manner similar to that described in Ref. Ex. 1, but starting with triphenylphosphine (104.8 g), diisopropyl azodicarboxylate (80.8 g) and (3R)-3-hydroxyquinuclidine (25.7 g). (3S)-3-(Acetylthio)quinuclidine (30 g) is thereby obtained in the form of a yellow oil [Rf = 0.2; eluant: methylene chloride/methanol (90:10 by volume)]. According to R.P. Volante, Tet. Let., 22 (33), 3119 (1981) the 3 carbon of (R) configuration is converted to carbon of (S) configuration during the reaction.

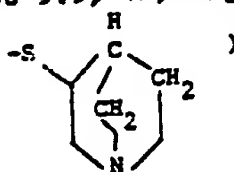
(3R)-3-Hydroxyquinuclidine is prepared according to the method described by B. RINGDAHL, B. RESUL and R. DAHLBOM, Acta Pharma. Suec. 16, 281 (1979).

### REFERENCE EXAMPLE 3

Working in a manner similar to that described in Ref. Ex. 1, but starting with 5 $\beta$ -methylenepristinamycin IA (6.15 g) and (3R)-3-mercaptoquinuclidine (1 g), and after a purification by flash chromatography, collecting 40-cc fractions (eluant: methylene chloride/methanol (85:15 by volume)), and concentration to dryness of the fractions 20 to 30, 5 $\beta$ -{[(3R)-3-quinuclidinyl]thiomethyl}pristinamycin IA (2 g) is obtained in the form of a beige powder, m.p. about 200°C.

NMR spectrum

0.58 (dd, J = 15 and 5.5, 1H, 5B<sub>2</sub>)  
1.5 t 2.2 (c,

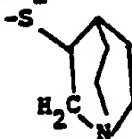


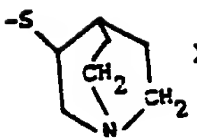
2.30 (c, 1H, 5 $\delta$ )

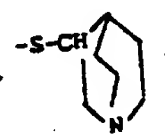
2.35 (d, J = 15, 1H, 5B<sub>1</sub>)

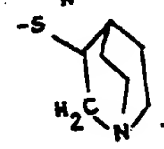
2.50 (dd, 1H of -CH<sub>2</sub>S-)

2.60 (dd, 1H, 5 $\epsilon$ <sub>2</sub>)

5 2.78 (c, 1H of )

2.90 to 3.10 (c, 1H of -CH<sub>2</sub>-S- and )

3.15 (c, 1H, )

3.48 (c, 1H of )

4.95 (dd, 1H, 5 $\epsilon$ <sub>1</sub>)

10 5.28 (c, 2H, 5 $\alpha$  and 4 $\alpha$ )

7.87 (c, 1H x 0.85, the H<sub>6</sub> of the 1st isomer)

7.93 (c, 1H x 0.15, the H<sub>6</sub> of the 2nd isomer)

5 $\delta$ -[[[(3R)-3-quinuclidinyl]thiomethyl]pristina-

mycin IA may be recrystallized in the following manner:

15 5 $\delta$ -[[[(3R)-3-quinuclidinyl]thiomethyl]pristina-

mycin IA (14.15 g) is dissolved in methanol (75 cc).

Distilled water (4 cc) is added to this solution, which

is then left to crystallize at 4°C. The crystals ob-

20 tained are filtered off and then rinsed with a methanol/

water (95:5 by volume) mixture (4 x 10 cc). After being

dried under reduced pressure (90 Pa) at 42°C, white crys-

tals (10.22 g) are obtained, m.p. about 190°C.

(3R)-3-Mercaptoquinuclidine may be obtained in a

manner similar to that described in Ref. Ex.2, but starting with (3R)-3-(acetylthio)quinuclidine (32.5 g) and 10N aqueous sodium hydroxide solution (35 cc); (3R)-3-mercaptoquinuclidine (11.5 g) is obtained in the form of 5 white crystals which melt at 45°C and distil at 90°C under 830 Pa ( $\alpha_D^{20} = +121^\circ$ ,  $c = 1.1$ , methanol).

(3R)-3-(Acetylthio)quinuclidine may be obtained in a manner similar to that described in Ref. Ex. 1, but starting with triphenylphosphine (104.8 g), diisopropyl 10 azodicarboxylate (80.8 g) and (3S)-3-hydroxyquinuclidine (25.7 g). (3R)-3-(Acetylthio)quinuclidine (33.8 g) is thereby obtained in the form of a pale brown oil [Rf = 0.4; eluant: methylene chloride/methanol (80:20 by volume)].

(3S)-3-Hydroxyquinuclidine is prepared according 15 to the method described by B. RINGDAHL et al., Acta Pharm. Suec. 16, 281 (1979).

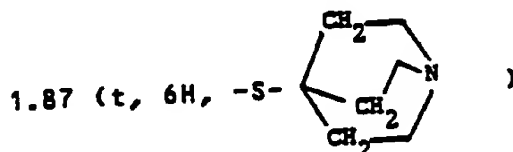
#### REFERENCE EXAMPLE 4

Working in a manner similar to that described in Ref. Ex.1, but starting with 5 $\delta$ -methylenepristinamycin 1A 20 (3.5 g) and 4-mercaptoquinuclidine (0.6 g) and after concentration to dryness, a solid is obtained which is stirred in ethyl ether. After filtration, a beige solid (3.6 g) is isolated, and purified by flash chromatography, collecting 50-cc fractions [eluant: methylene chloride/ 25 methanol (85:15 by volume)]. After concentration to dryness of fractions 19 to 35, washing with ethyl ether, filtration and then drying of the resulting solid under

reduced pressure (2.7 kPa) at 20°C, 56-[(4-quinuclidinyl)-thiomethyl]pristinamycin 1A (1.2 g) is obtained in the form of an off-white powder, m.p. about 200°C.

NMR spectrum (2 isomers in respect of the 56 carbon, in the ratio 85:15 approximately):

0.62 (dd, J = 15 and 5.5, 1H, 5B2)

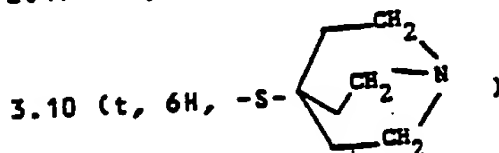


2.20 (c, 1H, 56)

2.28 (c, 1H, -CH2-S-)

10 2.35 (d, J = 15, 1H, 5B1)

2.47 (dd, 1H, 5E2)



3.22 (dd, 1H, -CH2-S-)

5.01 (dd, 1H, 5E1)

15 5.29 (broad d, J = 5.5, 5α)

7.86 (c, 0.85H, the H6 of the preponderant isomer)

7.92 (c, 0.15H, the H6 of the minority isomer)

4-Mercaptoquinuclidine may be obtained according to the method described by A. GROB, *Helv. Chim. Acta*, 57, 202339 (1974).

#### REFERENCE EXAMPLE 5

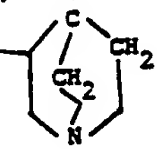
The procedure is similar to that described in Ref. Ex. 1, but starting with 56-methylenevirginiamycin S (1.2 g) in methanol

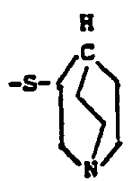
(20cc) and (3R)-3-mercaptoquinuclidine (0.21 g). After purification by flash chromatography, collecting 10-cc fractions [eluant: methylene chloride/methanol (95:5 by volume) up to the fraction 35, then methylene chloride/

5 methanol (80:20 by volume)], concentration to dryness of the fractions 47 to 55 and drying under reduced pressure (2.7 kPa) at 30°C, 5 $\delta$ -[[ (3R)-3-quinuclidinyl]thiomethyl]-virginiamycin S (0.6 g) is obtained in the form of an off-white powder, m.p. about 185°C.

10 NMR spectrum (2 isomers in respect of the 5 $\delta$  carbon, in the ratio 80:20 approximately):

0.4 (dd, J = 15 and 5.5, 1H, 5B<sub>2</sub>)

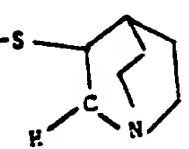
1.5 to 2.2 (c, 5H, -S-, 5 $\delta$ )

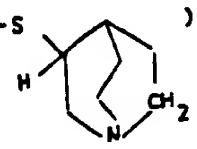
2 (c, 1H, -S-)

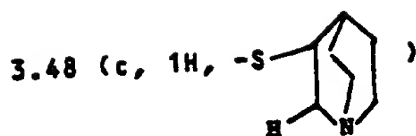
15 2.34 (d, J = 15, 1H, 5B<sub>1</sub>)

2.52 (dd, 1H of -CH<sub>2</sub>S-)

2.63 (dd, 1H, 5 $\epsilon$ <sub>2</sub>)

2.78 (dd, 1H of -S-)

2.85 t 3.15 (c, 1H of -CH<sub>2</sub>-S- and -S-)



4.94 (dd, 1H, 5B<sub>1</sub>)

5.27 (broad d, J = 5, 1H, 5a)

7.82 (dd, J = 4 and 1, the H<sub>6</sub> of the 1st isomer)

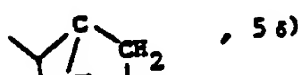
7.9 (dd, J = 4 and 1, the H<sub>6</sub> of the 2nd isomer)

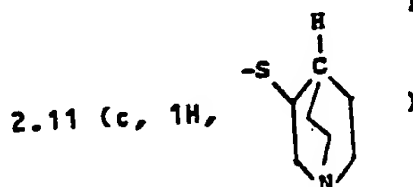
# REFERENCE EXAMPLE 6

The procedure is similar to that described in Ref. Ex. 1, but starting with 5δ-methylenevirginiamycin S (1.1g) in methanol (20 cc) and (3S)-3-mercaptoquinuclidine (0.19 g). After  
10 purification by flash chromatography, collecting 10-cc fractions [eluant: methylene chloride/methanol (90:10 by volume)], concentration to dryness of fractions 19 to 32 and drying under reduced pressure (2.7 kPa) at 30°C, 5δ-  
[(3S)-3-quinuclidinyl]thiomethyl virginiamycin S (0.5 g)  
15 is obtained in the form of a pale yellow powder, m.p. about 190°C.

NMR spectrum (2 isomers in respect of the 5δ carbon, in the ratio 85:15 approximately):

0.39 (dd, J = 15 and 5, 1H, 5B<sub>2</sub>)

1.5 to 2.3 (c, 5H, -S , 5δ)



2.34 (d, J = 15, 1H, 5B<sub>1</sub>)

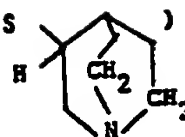
2.52 (dd, 1H of -CH<sub>2</sub>S-)

2.64 (dd, 1H, 5 $\epsilon$ <sub>2</sub>)

2.66 (dd, 1H of -S



2.90 to 3.2 (c, 6H, 1H of -CH<sub>2</sub>-S-, and -S



3.3 to 3.5 (c, 1H of -S



5

4.95 (dd, 1H, 5 $\epsilon$ <sub>1</sub>)

5.27 (broad d, 1H, 5 $\alpha$ )

7.80 (dd, J = 4 and 1, 1H x 0.85, the H<sub>6</sub> of the  
1st isomer)

7.90 (dd, J = 4 and 1, 1H x 0.15, the H<sub>6</sub> of the  
2nd isomer)

10

#### REFERENCE EXAMPLE 7

Working in a manner similar to that described in Ref. Ex.2, but starting with (3S)-3-mercaptoquinuclidine (1.62 g) and stirring at -20°C for 20 hours, a beige  
15 meringue-like product (11.4 g) is obtained after concentration to dryness under reduced pressure (2.7 kPa) at 30°C, and this is stirred in diethyl ether (100 cc), filtered and then rinsed with the same solvent (3 x 20 cc). This product may be recrystallized in acetone as described  
20 in Ref. Ex.2, to give 56-[[[(3S)-3-quinuclidinyl]thiomethyl]-pristinamycin I<sub>A</sub> (6.6 g) in the form of white crystals, m.p. about 198-200°C, the characteristics which are identical to those of the product obtained in Ref. Ex.2, and



containing 3 % of minority isomer assayed by HPLC.

REFERENCE EXAMPLE 8

(3S)-3-Mercaptoquinuclidine (0.18 g) dissolved in acetone (5 cc) is added at  $-20^{\circ}\text{C}$  in the course of 1 hour 5 to a solution of 5 $\delta$ -methylenepristinamycin IA (1 g) in acetone (20 cc). After 18 hours' stirring at  $-20^{\circ}\text{C}$ , the reaction mixture is filtered and the solid rinsed with acetone (3 x 2 cc). After being dried in the air, 5 $\delta$ -  
10  $\{[(3S)-3\text{-quinuclidinyl}] \text{thiomethyl}\}$ pristinamycin IA (0.6 g) is obtained in the form of white crystals, m.p. about  $190^{\circ}\text{C}$ , the characteristics of which are identical to those of the product obtained in Ref. Ex.2 and containing 3 % of the minority 5 $\delta$ -isomer assayed by HPLC.

REFERENCE EXAMPLE 9

15 (3S)-3-Mercaptoquinuclidine (0.16 g) dissolved in acetone (5 cc) is added at  $-78^{\circ}\text{C}$  to a solution of 5 $\delta$ -methylenepristinamycin IA (1.22 g) in acetone (15 cc), and the solution obtained is stirred under nitrogen for 24 hours at  $-78^{\circ}\text{C}$ . The reaction mixture is then concen-  
20 trated to dryness under reduced pressure (2.7 kPa) at  $30^{\circ}\text{C}$  to give 1.4 g of a cream-white solid containing 5 % of minority isomer assayed by HPLC and having characteristics identical to those of the product obtained in Ref. Ex. 2.

The present invention also provides pharmaceutical compositions comprising a compound of the formula (I), in the free form or, preferably, in the form of an addition salt with a pharmaceutically acceptable acid, 5 optionally in association with a known synergist or, preferably, a synergist of the formula (XI) or (XIv) it being possible for the composition or association also to contain any other pharmaceutically compatible product which is inert or physiologically 10 active. The compositions of the invention can be

administered by parenteral, oral, rectal or topical route.

Sterile compositions for parenteral administration can be, preferably, aqueous or nonaqueous solutions, suspensions or emulsions. Water, propylene glycol, a poly-  
5 (ethylene glycol), vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents, can be used as a solvent or vehicle. These compositions can also contain adju-  
vants, especially wetting agents, isotonizing agents,  
10 emulsifiers, dispersants and stabilizers. Sterilization can be carried out in various ways, for example by an asepticizing filtration, by adding sterilizing agents to the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions  
15 which can be dissolved in an injectable sterile medium at the time of use.

Tablets, pills, powders or granules can be employed as solid compositions for oral administration. In these compositions, the active product according to the invention  
20 (optionally combined with another pharmaceutically compatible product) is mixed with one or more inert diluents or adjuvants such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, for example a lubricant such as magnesium stearate.

25 Pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents such as water or paraffin oil can be used as liquid

compositions for oral administration. These compositions can also comprise substances other than the diluents, for example wetting agents, sweeteners or flavourings.

5        Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active substance, excipients such as cocoa butter, semi-synthetic glycerides or poly(ethylene glycols).

10       Compositions for topical administration can be, for example, creams, salves, lotions, eye lotions, mouth washes, nasal drops or aerosols.

         In general, when the compounds of general formula (I) are associated with known synergists, or  
15 synergists described in EP 133096 or 133097 or of formula (XIV) the ratio is from 10:90% to 90:10% preferably 50% to 50% wt/wt.

         In human therapy, the products according to the invention, which may be combined with known  
20 synergists or preferably with synergists of general formula (XI) or (XIV) are especially useful in the treatment of infections of a bacterial origin. The dosages depend on the required effect and on the duration of treatment; for an adult, they are generally  
25 between 500 and 2000 mg per day by parenteral route, especially by an intravenous route such as a slow

perfusion, the dosage of known synergistin or synergistin of general formula (XI) or (XIV) if present itself being between 500 and 2000 mg per day.

As a general rule, the practitioner will determine the dosage which he or she considers the most suitable, depending on the age, weight and all the other individual characteristics of the subject to be treated.

The following examples, given without implying any limitation, illustrates the compositions according to the invention.

EXAMPLE A

An injectable solution for perfusion, containing 5 g/l of active product having the following composition is prepared:

- 15 - 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A) 5 g
- 0.1 N aqueous solution of hydrochloric acid 49 cc
- distilled water q.s. 1000 cc

EXAMPLE B

20 An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

- 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>) 0.6 g
- 25 - 5 δ-[2-(4-methyl-1-piperazinyl)ethyl]-thiomethylpristinamycin I<sub>A</sub> 0.4g
- 0.1 N aqueous solution of hydrochloric acid 12.7 cc
- distilled water q.s. 1000 cc

EXAMPLE C

An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

- 5 - 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>) 0.6 g
- 5δ-[3(S)-quinuclidinyl-thiomethylpristinamycin I<sub>A</sub> 0.4g
- 0.1 N aqueous solution of hydrochloric acid 12.7 cc
- 10 - distilled water q.s. 1000 cc

EXAMPLE D

An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

- 15 - 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A ) 0.6 g
- 5δ-[3(R)-quinuclidinyl-thiomethylpristinamycin I<sub>A</sub> 0.4g
- 0.1 N aqueous solution of hydrochloric acid 12.7 cc
- 20 - distilled water q.s. 1000 cc

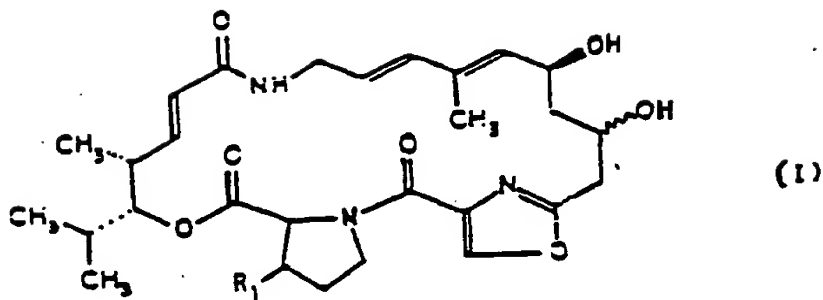
EXAMPLE E

An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

- 25 - 16-deoxy-26-(2-diisopropylaminoethyl)thio-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A) 0.6 g
- 5δ-[3-quinuclidinyl-thiomethylpristinamycin I<sub>A</sub> 0.4g
- 0.1 N aqueous solution of hydrochloric acid 12.7 cc
- 30 - distilled water q.s. 1000 cc

CLAIMS

1. A pristinamycin II<sub>B</sub> derivative of the formula:



in which R<sub>1</sub> denotes

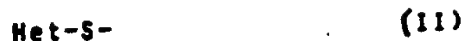
1. an alkylthio radical containing 1 to 5 carbon atoms, substituted

i) with one or two alkylamino or dialkylamino radicals in which the alkyl portions, which contain 1 to 5 carbon atoms, can optionally form, together with the nitrogen atom to which they are linked, a saturated heterocyclic radical chosen from 1-pyrrolidinyl, piperidino, 1-azetidiny, 1-azepinyl, morpholino, thiomorpholino and 1-piperazinyl (optionally substituted with an alkyl radical containing 1 to 5 carbon atoms), or alternatively

ii) with a 2- or 3-pyrrolidinyl, 2-, 3- or 4-piperidyl, 2- or 3-azetidiny or 2-, 3- or 4-azepinyl

radical,

2. a radical of general formula:



in which Het denotes a 3-pyrrolidinyl, 3- or 4-piperidyl, 3-azetidinyll or 3- or 4-azepinyl radical, optionally substituted with an alkyl radical containing 1 to 5 carbon atoms,

3. a dialkylamino radical in which the alkyl portions, which contain 1 to 5 carbon atoms, can optionally form, together with the nitrogen atom to which they are linked, a saturated heterocyclic radical chosen from 1-pyrrolidinyl, piperidino, 1-azetidinyll, 1-azepinyl, morpholino, thio-morpholino and 1-piperazinyl (optionally substituted with an alkyl radical containing 1 to 5 carbon atoms),

4. a radical of general formula:



in which R<sub>2</sub> denotes

i) either a 4- to 7-membered nitrogen-containing heterocyclic radical optionally containing one or more other hetero atoms chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, and optionally substituted with an alkyl radical,

ii) or an alkyl chain containing 2 to 4 carbon atoms and substituted with 1 or 2 radicals chosen from phenyl, cycloalkylamino or N-alkyl-N-cycloalkylamino containing 3 to 6 ring atoms, alkylamino, dialkylamino or



dialkylcarbamoyloxy, the alkyl portions of these last 2 radicals optionally being able to form, with the nitrogen atom to which they are attached, a 4- to 7-membered saturated or unsaturated heterocyclic radical optionally containing another hetero atom chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, and optionally substituted with an alkyl radical), or substituted with one or more 4- to 7-membered nitrogen-containing heterocyclic radicals optionally containing 1 or 2 other hetero atoms chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, these heterocyclic radicals optionally being substituted with an alkyl radical, the said heterocyclic radicals being attached to the chain which bears them via a carbon atom, with the proviso that at least one of the substituents borne by the above alkyl chain is a nitrogen-containing substituent capable of forming salts, or [(S)-1-methyl-2-pyrrolidinyl]methyl, and the symbol n equals 1 or 2,

5. an alkylamino radical which is optionally substituted by a hydroxy (e.g. the 2-hydroxyethylamino radical) or alkylamino or

dialkylamino, the alkyl portions of this last radical optionally being able to form, with the nitrogen atom to which they are attached, a 4- to 7-membered saturated or unsaturated heterocyclic radical optionally containing another hetero atom chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, and optionally substituted with an alkyl radical), or substituted with one or more 4- to 7-membered nitrogen-containing heterocyclic radicals optionally containing 1 or 2 other hetero atoms chosen from nitrogen, oxygen or sulphur in the state of sulfoxide or sulphone, these heterocyclic radicals optionally being substituted with an alkyl radical, the said heterocyclic radicals being attached to the chain which bears them via a carbon atom,

with the proviso that the alkyl radicals and portions mentioned above are linear or branched and contain, except where otherwise stated, 1 to 10 carbon atoms, and its isomeric forms and their mixtures.

2. 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

3. 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16beta-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

4. 16-deoxy-26-(2-diisopropylaminoethyl) thio-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

5. 16-deoxy-26-(2-diisopropylaminoethyl) thio-16beta-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

6. 16-deoxy-26-(2-diisopropylaminoethyl)-sulphinyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>) and its isomers and salts.

7. 16-deoxy-26-(2-diisopropylaminoethyl)-sulphinyl-16beta-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>) and its isomers and salts.

8. 16-deoxy-26-(2-diethylaminoethyl) thio-16beta-hydroxy-pristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

9. 16-deoxy-26-(2-diethylaminoethyl) thio-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

10. 16-deoxy-26-(2-diethylaminoethyl) sulphinyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A<sub>2</sub>) and its isomers and salts.

11. 16-deoxy-26-(2-diethylaminoethyl) sulphinyl-16alpha-hydroxypristinamycin II<sub>B</sub> (isomers A<sub>1</sub> + A<sub>2</sub>) and its isomers and salts.

12. 16-deoxy-26-(2-diethylaminoethyl)sulphonyl-16beta-hydroxypristinamycin (isomer A<sub>2</sub>) and its isomers and salts.

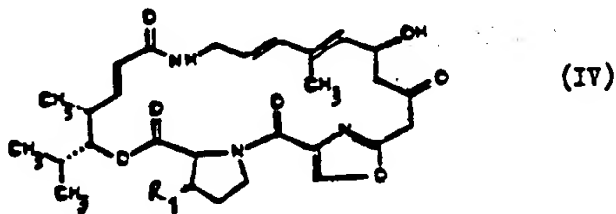
13. 16-deoxy-26-ethylamino-16beta-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

14. 16-deoxy-26-ethylamino-16alpha-hydroxypristinamycin II<sub>B</sub> (isomer A) and its isomers and salts.

15. 16-deoxy-26-(2-diethylaminoethyl)amino-16alpha-hydroxypristinamycin II<sub>B</sub> and its isomers and salts.

16. 16-deoxy-26-(2-diethylaminoethyl)amino-16beta-hydroxypristinamycin II<sub>B</sub> and its isomers and salts.

17. Process for the preparation of a compound as claimed in claim 1 which comprises reducing a compound of the general formula:



where R<sub>1</sub> is as defined in claim 1.

in which  $R_2$  is defined as above, it being understood that where  $R_2$  contains a sulphur containing heterocyclic ring the sulphur atom can be in the form of a sulphide, sulphoxide or sulphone.

20. Process for the preparation of a compound as claimed in claim 1 substantially as described in any of the foregoing Examples.

21. A pristinamycin  $II_B$  derivative as claimed in claim 1 when prepared by a process as claimed in any one of claims 17 to 20.

22. A pharmaceutical composition comprising a pristinamycin  $II_B$  derivative as claimed in any one of claims 1 to 16 and 21 in association with an inert pharmaceutically acceptable carrier or coating and/or pristinamycin  $I_A$ , virginiamycin S, or a soluble synergistin derivative of general formula XI as hereinbefore defined.



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